Title: An Open-Label, Dose-Escalation, Phase 1 Study of the Oral Formulation of MLN9708 Administered Weekly in Adult Patients With Relapsed or Refractory Light-Chain (AL) Amyloidosis Who Require Further Treatment

NCT Number: NCT01318902

Protocol Approve Date: 22 December 2014

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CLINICAL STUDY PROTOCOL C16007 AMENDMENT 6

MLN9708

An Open-Label, Dose-Escalation, Phase 1 Study of the Oral Formulation of MLN9708 Administered Weekly in Adult Patients With Relapsed or Refractory Light-Chain (AL) Amyloidosis Who Require Further Treatment

Protocol Number:	C16007
Indication:	Amyloidosis
Phase:	1
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2010-022497-13
Therapeutic Area:	Oncology

Protocol History

Original		31 August 2010
Amendment 1		14 December 2010
Amendment 2	*for use in Italy only*	25 May 2011
Amendment 3		19 July 2011
Amendment 4	*for use in Italy only*	02 August 2011
Amendment 5		02 December 2014
Amendment 6	*for use in Italy only*	22 December 2014

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Note: If this document was approved electronically, the electronic approval signatures may be found at the end of the document.

Approved by:

PPD

Rationale for Amendment 6

This amendment allows for the following: a longer follow-up period for overall survival, an extension for a rollover study should one become available, and flexibility in laboratory evaluations as per standard of care.

Purposes for Amendment 6

The purposes of this amendment are to:

- Update the cover page with current signatories.
- Update the duration of the study and overall survival time point.
- Update the hematology and chemistry laboratory evaluation schedule.
- Update the SAE reporting contact information.
- Update the product complaint reporting contact information.
- Correct typographical errors, punctuation, grammar, and formatting.

For specific examples of changes in text and where the changes are located, see Section 15.12.

PROTOCOL SUMMARY

Study Title: An Open-Label, Dose-Escalation, Phase 1 Study of the Oral Formulation of MLN9708 Administered Weekly in Adult Patients With Relapsed or Refractory Light-Chain (AL) Amyloidosis Who Require Further Treatment

Study Phase: 1

Number of Patients: Overall, as many as 50 patients will be enrolled in the study.

Study Objectives

Primary Objectives

- To determine the safety, tolerability, and maximum tolerated dose (MTD) of oral MLN9708 administered weekly in patients with previously treated relapsed or refractory light-chain (AL) amyloidosis
- To determine the recommended phase 2 dose (RP2D) of oral MLN9708 administered weekly

Secondary Objectives

- To characterize the plasma PK and whole blood pharmacodynamic effect of MLN9708 in this patient population
- To assess the rate of organ response and organ improvement according to standardized criteria
- To assess overall hematologic response rate (complete response [CR], very good partial response [VGPR], and partial response [PR])
- To assess time to hematologic and organ response, respectively
- To assess duration of hematologic and organ response, respectively
- To determine time to hematologic and organ disease progression, respectively
- To assess progression free survival (PFS)
- To assess overall survival including 1-year survival rate

Exploratory Objectives

CCI

[redacted]

Overview of Study Design:

The study will include patients with previously treated systemic AL amyloidosis who require further therapy and will be aimed at determining the safety profile and the MTD/RP2D of MLN9708 administered orally. A 3 + 3 dose-escalation scheme will be implemented. Patients will receive escalating doses of MLN9708 PO on Days 1, 8, and 15 in a 28-day cycle in the absence of disease progression or unacceptable toxicity. If there is no hematologic response (CR + VGPR + PR) after completion of 3 cycles of single-agent MLN9708, dexamethasone will be added on Days 1 to 4 of every cycle (Days1-4 every 28 days) beginning with Cycle 4. The patient's response status will be reassessed after 3 additional cycles; if there is no hematologic response at that time, the patient will be removed from treatment and followed for survival.

The estimated safe starting dose of MLN9708 will be selected from the dose-escalation portion of

the C16004 study, a phase 1 study of weekly dosing in patients with relapsed and refractory multiple myeloma. The starting dose will be at least 1 dose level below the C16004 MTD (if it has been reached by the time this study starts) and, if not, then a dose level completed without documented dose-limiting toxicity (DLT).

DLTs will be assessed in Cycle 1 only. In the context of emerging clinical data of single-agent MLN9708, dose-escalation of MLN9708 will continue until the MTD has been identified or a maximum planned dose (MPD) is determined to be safe.

Once the MTD/RP2D has been established, 2 expansion cohorts of patients with relapsed or refractory amyloidosis, including approximately 10 proteasome inhibitor-naïve patients and approximately 16 proteasome inhibitor-exposed patients, will be treated at the MTD/RP2D to more fully characterize the safety, tolerability, and efficacy of MLN9708, and the PK and pharmacodynamics of MLN9708 in this patient population. As many as 30 patients will be enrolled in the dose-escalation portion of the study, and as many as 20 additional patients (26 in total, including 6 patients from the dose-escalation portion) will be enrolled in the expansion cohorts.

Toxicity will be evaluated according to the investigators' documentation of adverse events (AEs) using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. AEs will be assessed, and laboratory values, vital signs, and ECGs will be obtained to evaluate the safety and tolerability of MLN9708.

Patients will be evaluated at scheduled visits over 4 study periods: Screening, Treatment, End of Treatment (EOT), and Follow-up (progression-free and overall survival). Patients will discontinue treatment if they experience PD or unacceptable toxicity. The maximum duration of treatment with either single-agent MLN9708 or MLN9708 plus dexamethasone, however, will be 12 cycles unless after discussion between the investigator and the sponsor, it is determined that a patient would derive benefit from continued therapy beyond 12 cycles.

The primary determinant of response for the purpose of continuing treatment is the hematologic response. Response will be determined according to standardized criteria. Hematologic response assessments are conducted after every cycle during treatment, at the end of treatment visit, and then every 6 weeks thereafter until disease progression or initiation of subsequent antineoplastic therapy. A bone marrow aspirate and biopsy are to be obtained at the Screening visit and may be repeated at the discretion of the investigator as clinically indicated and if CR is documented by other parameters in the standardized criteria.

Amyloid-related organ assessments are to be performed for all patients at screening; after Cycles 3, 6, 9, and 12; every 6 months thereafter until disease progression or the initiation of subsequent antineoplastic therapy; and at the End-of-Treatment visit. An evaluation of disease response according to standardized criteria will be performed at regular predefined intervals during treatment and then at regular intervals during follow up. Radiological evaluations (skeletal surveys, chest X-rays, computed tomography [CT] scan, or magnetic resonance imaging [MRI]), echocardiograms, blood samples and 24-hour urine collections (M-protein quantification, serum free light chain assay, immunofixation of serum and urine, quantification of immunoglobulins, serum cardiac markers) and bone marrow biopsy and aspirates will be employed to assess the status of the patient's disease response.

Quality of life (QOL) will be assessed only for patients in the expansion cohorts using the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC-QLQ-C30.

A blood sample will be collected for preparation of genomic deoxyribonucleic acid that will be used, as needed, to assess potential relationships CCI [redacted], clinical response, and safety.

Electrocardiograms will be acquired on Day 1 of Cycles 1 through 12 and at EOT and a 24-hour Holter monitor will be used at screening.

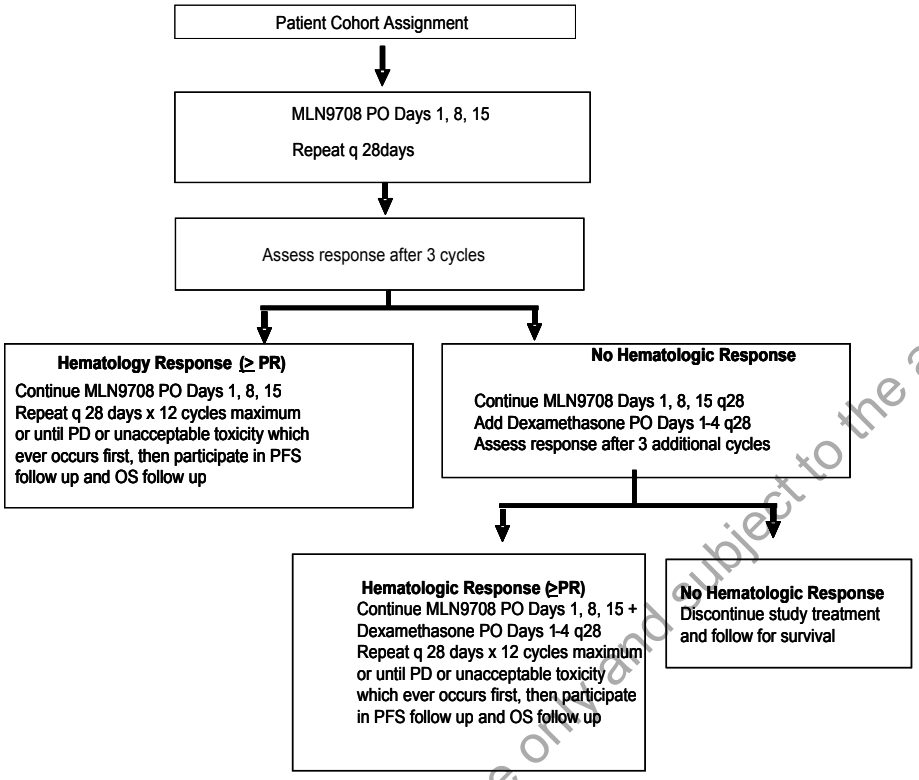
Study Population:

Adult patients 18 years or older with biopsy-proven systemic AL amyloidosis with relapsed or refractory disease after at least 1 prior therapy that, in the investigator's opinion, requires further treatment. If a patient has received a transplant as his/her first therapy, he/she must be at least 3 months posttransplantation and recovered from the side effects of the stem cell transplant. Patients who were not candidates for high-dose therapy and were unable to tolerate an alkylating agent plus a corticosteroid (eg, melphalan plus prednisone) or patients who are intolerant to an alternative prior therapy after receiving at least 1 cycle of such therapy because of severe adverse events (eg, hypersensitivity reaction) can be considered for enrollment after discussion with the Millennium clinician.

Duration of Study: The duration of enrollment will be approximately 24 months.

It is anticipated that this study will last for approximately 84 months. The duration of follow-up for OS will be 60 months after the last patient enters treatment. Treatment may be continued in this study or in a MLN9708 rollover study, if and when such a study is made available, upon request by the investigator and agreement by the project clinician.

Study Overview Diagram



Schedule of Events

Study Procedures	Screening[a]	Treatment Period				End of Treatment[d]	Follow-up	
		CYCLES 1 -12[b]						
	Days	Days					PFS[e] (± 1 wk)	OS[f] (± 1 wk)
	-28 to -1	1[c]	8	15	Rest Period 22 to 28		Every 6 weeks	Every 12 weeks
Informed Consent	X							
Inclusion/Exclusion criteria	X							
Demographics	X							
Complete Medical History, including AL amyloidosis treatment history, neurologic history, and cardiac medical history	X							
12-lead ECG (RR, PR, QRS, QT, QTc, and waveforms)	X	X				X		
24-hour Holter monitor[g]	X							
Physical Examination	X	X[h]				X	Per MD practice	
ECOG Performance Status	X	X[i]				X		
Vital Signs	X	X				X	Per MD practice	
Height	X							
Weight (kg)	X	X				X		
Pregnancy Test[j]	X	X						
Hematology[k]	X	X	X	X	X	X		
Clinical Chemistry[k]	X	X	X	X	X	X		
Urinalysis	X					X		
24-hour urine collection for creatinine and total protein	X				X[l]	X	X[l]	
Coagulation studies (PT/INR; PTT)[m]	X							

Study Procedures	Screening[a]	Treatment Period				End of Treatment[d]	Follow-up	
		CYCLES 1 -12[b]						
	Days	Days					PFS[e] (± 1 wk)	OS[f] (± 1 wk)
	-28 to -1	1[c]	8	15	Rest Period 22 to 28		Every 6 weeks	Every 12 weeks
Thyroid stimulating hormone (TSH); random cortisol level	X							
Blood Sample for Genotyping	X							
Neurologic examination	X	X				X	X[e]	
QOL Assessment[n]	X				X	X		
PK and Whole blood 20S proteasome activity		See table below for detailed sampling schedule						
Response Assessment								
Hematological Disease Response Assessment[o]					X	X	X	
β2-microglobulin	X							
M-protein measurements (SPEP)	X				X	X	X	
M-protein measurements (UPEP [24-hour urine collection])	X				X	X	X	
Serum free light chain assay	X				X	X	X	
Immunofixation - serum and urine	X				X	X	X	
Quantification of Ig	X				X	X	X	
Bone marrow biopsy/aspiration	X[p]				X[q]	X	X[q]	
Skeletal Survey[r]	X				X	X	X	
Amyloid-related organ assessment[s,t]	X							
Posteroanterior and lateral CXR	X							
CT or MRI scans as indicated to assess organ involvement (eg, lung; liver)[s,u]	X							
Echocardiogram[s]	X				X	X	X	
Estimates of interventricular septal and posterior wall thickness[s]	X				X	X	X	

Study Procedures	Screening[a]	Treatment Period				End of Treatment[d]	Follow-up	
		CYCLES 1 -12[b]						
	Days	Days					PFS[e] (± 1 wk)	OS[f] (± 1 wk)
	-28 to -1	1[c]	8	15	Rest Period 22 to 28		Every 6 weeks	Every 12 weeks
Serum cardiac markers (NT-proBNP, BNP, troponin T or I)[s]	X				X	X	X	
NYHA classification	X	X				X	X	
Adverse Events		Recorded from the first dose of study drug through 30 days after last dose of study drug or until the initiation of subsequent antineoplastic therapy						
Serious Adverse Events	Recorded from the time informed consent is signed through 30 days after the last dose of study drug							
Concomitant Medications/Procedures		Recorded from the first dose of study drug through 30 days after last dose of study drug or until the intitiation of subsequent antineoplastic therapy						
Study Drug Administration								
MLN9708		X	X	X				
Dexamethasone (only if no response after 3 cycles of single-agent MLN9708)		X						
Survival								X

Abbreviations: BNP = B-type natriuretic peptide; CT = computed tomography CXR = chest X-ray; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMG = electromyography; EOT = end of treatment; Ig = immunoglobulin; INR = international normalized ration; MRI = magnetic resonance imaging; NT-proBNP = N-terminal proBNP; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PT = prothombin time; PTT = partial thromboplastin time; QOL = quality of life; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

a Evaluations including CT scans, MRIs, and skeletal surveys may be performed within 8 weeks of the first dose of study drug.

b One complete cycle is 28 days. In order to begin a new cycle of treatment, certain criteria must be met (see Section 6.5.2). Patients who do not continue study treatment dosing after Cycle 1 must complete the EOT and follow-up assessments.

c All evaluations/procedures are to be conducted on Day 1 of the stated cycle before dosing or within 3 days before the first dose of drug unless otherwise specified.

d Patients who do not continue treatment must complete the EOT assessments, which should occur at least 30 days after the last dose of study drug or prior to

Study Procedures	Screening[a]	Treatment Period				End of Treatment[d]	Follow-up	
		CYCLES 1 -12[b]						
	Days	Days					PFS[e] (± 1 wk)	OS[f] (± 1 wk)
	-28 to -1	1[c]	8	15	Rest Period 22 to 28		Every 6 weeks	Every 12 weeks

the initiation of subsequent antineoplastic therapy.

e Conducted from EOT until occurrence of PD or the initiation of subsequent antineoplastic therapy. If a patient comes off treatment due to PD, they should continue to be followed for OS long-term follow-up. Hematologic response assessments should be conducted every 6 weeks (± 1 week) during PFS follow-up while amyloid organ response assessments should be conducted every 6 months, including a neurologic examination in patients with persistent neurologic symptoms and clinical examinations in patients with persistent symptoms thought by the investigator to be amyloid-disease related (see Section 7.5.12).

f Conducted every 12 weeks (± 1 week) after PD or the initiation of subsequent antineoplastic therapy. Data may be collected by methods that include but are not limited to telephone, e-mail, mail, and social security indexes.

g 24-hour Holter monitor, to be performed at screening, and at any time the physician believes it is medically appropriate.

h A full physical exam will occur every 3 cycles. Symptom-directed assessments will be conducted per standard clinical practice.

i Should occur every 3 cycles.

j A serum pregnancy test will be performed for women of childbearing potential during screening and predose on Cycle 1, Day 1. The serum pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the first dose of MLN9708 is administered.

k Hematology and chemistry panels may be collected up to 3 days prior to dosing. Criteria for retreatment are provided in Section 6.5.2. After 24 cycles on treatment, hematology and chemistry laboratory evaluations may be done to monitor the patient according to standard clinical practice per the treating physician.

l Repeat as clinically indicated by change in serum creatinine. Creatinine clearance will be calculated based on a 24-hour urine collection at screening. eGFR will be calculated according to the equations in Section 15.1. 24-hour urine for protein is required to assess amyloid renal involvement/ response.

m If abnormal, a diagnostic work up should be performed and the patient treated and stabilized before administering MLN9708. PT/INR and PTT may be repeated during the treatment period at the discretion of the investigator if bleeding occurs or as clinically indicated.

n Only for patients in the extension cohort after every cycle.

o Repeat every treatment cycle, at the EOT visit, and every 6 weeks during the PFS follow-up period.

p CCI [redacted]

q Bone marrow biopsy and aspirate should be repeated at the discretion of the investigator as clinically indicated and if response is documented by other parameters, and at EOT. Immunohistochemistry of dominant clonal plasma cells is recommended.

r To be performed at screening and at any time the physician believes there are symptoms or signs that suggest increased or new bone lesions. Plain films of symptomatic sites for signs or symptoms of new bone lesions may be obtained instead of a full skeletal survey. A PET-CT may be done at screening in

Study Procedures	Screening[a]	Treatment Period				End of Treatment[d]	Follow-up	
		CYCLES 1 -12[b]						
	Days	Days					PFS[e] (± 1 wk)	OS[f] (± 1 wk)
	-28 to -1	1[c]	8	15	Rest Period 22 to 28		Every 6 weeks	Every 12 weeks

place of a skeletal survey provided that the same modality for assessment is used throughout the study. If results are interpreted as abnormal, then repeat at the discretion of the investigator as clinically indicated. The same imaging modality used at screening should be used for all follow-up assessments.

s At baseline, Cycles 3, 6, 9, and 12, and every 6 months thereafter until disease progression or the initiation of subsequent antineoplastic therapy.

t The following tests should be included for organ assessments:
heart: NT-proBNP, BNP, troponin, echocardiography, physical examination;
kidney: 24-hour urine proteinuria, serum creatinine, eGFR, serum albumin;
liver: alkaline phosphatase, ALT, ultrasound/CT scan/ MRI (as indicated);
peripheral nervous system: patient reported symptoms, physical examination, electromyography (EMG; if indicated);
autonomic nervous system: patient reported symptoms, determination of postural hypotension;
gastrointestinal: patient reported symptoms;
soft tissue: physical examination, imaging as indicated

u If results are interpreted as abnormal, then repeat at the discretion of the investigator as clinically indicated except if being used to monitor amyloid liver involvement. The same imaging modality used at screening (CT/MRI) should be used for all follow-up assessments.

Pharmacokinetic & Pharmacodynamic Sampling (Cycle 1)

	Day 1[a]							Day 2	Day 8
	Minutes			Hours					
	Predose (within 1 hour of dosing)		30 (± 5)	1 (± 0.25)	2 (± 0.25)	4 (± 0.75)	6 (± 0.75)	24 (± 1.0)	168 (± 4.0) [prior to Day 8 dose]
PK (whole blood & plasma)	X	MLN9708	X	X	X	X	X	X	X
Whole blood 20S proteasome activity	X	MLN9708	X	X	X	X	X	X	X
	Day 15							**Day 16**	**Day 22**
	Minutes			Hours					
	Predose (within 1 hour of dosing)		30 (± 5)	1 (± 0.25)	2 (± 0.25)	4 (± 0.75)	6 (± 0.75)	24 (± 1.0)	168 (± 4.0)
PK (whole blood & plasma)	X	MLN9708	X	X	X	X	X	X	X
Whole blood 20S proteasome activity	X	MLN9708	X	X	X	X	X	X	X

The following samples will be collected at each time point: 1 blood sample (3 mL) for the determination of plasma concentrations of MLN2238, 1 blood sample (3 mL) for the determination of whole blood concentrations of MLN2238, and 1 blood sample (1 mL) for the measurement of whole blood 20S proteasome activity.

a Day 1, 2 and 8 samples are ONLY collected at the MTD; however, Day 15, 16 and 22 are collected for all patients.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
AL amyloidosis	primary systemic light chain amyloidosis
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-}24hr}$	area under the plasma concentration versus time curve zero to 24 hours
$AUC_{0\text{-}tau}$	area under the plasma concentration versus time curve zero to next dose
AV	atrioventriculatar
BCRP	breast cancer resistance protein
BNP	B-type natriuretic peptide
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CL	clearance
CL_b	blood clearance
CL_P	plasma clearance
C_{max}	maximum plasma concentration
CO_2	carbon dioxide
CR	complete response
CT	computed tomography
CYP	cytochrome P_{450}
DDI	drug-drug interaction
dFLC	serum differential free light chain concentration; difference between amyloid forming and non amyloid forming FLC
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate; eGFR according to the recently recommended CKD-EPI equation
E_{max}	maximum effect
EMG	electromyography
EORTC	European Organization for Research and Treatment of Cancer
EDC	electronic data capture
EOT	End of Treatment (visit)
F	bioavailability
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor

Abbreviation	Term
GI	gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMiDs	immunomodulatory drugs
IRB	Institutional Review Board
IV	intravenous; intravenously
K_i	inhibition constant
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MPD	maximum planned dose
MR	minimal response
MRI	magnetic resonance imaging
MRP2	multidrug resistance associated protein
msec	millisecond
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NT-proBNP	N-terminal proBNP
NYHA	New York Heart Association
OS	overall survival
PD	progressive disease (disease progression)
PFS	progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial response
QD	*quaque die*; each day; once daily
QLQ	Quality of Life Questionnaire
QLQ-C30	EORTC Core Quality of Life Questionnaire
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
RP2D	recommended phase 2 dose
SAE	serious adverse event
SCT	stem cell transplant

Abbreviation	Term
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event ; may or may not be treatment related
TE_{max}	time of occurrence of E_{max}
T_{max}	first time to maximum plasma concentration
ULN	upper limit of the normal range
US	United States
VGPR	very good partial response
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Primary systemic light chain (AL) amyloidosis is a progressive disorder caused by proteotoxic light chain proteins produced by a clonal plasma cell dyscrasia.[1, 2, 3] The plasma cell dyscrasia is characterized by monoclonal plasma cells in the bone marrow and the production of excess monoclonical immunoglobulin light-chains that tend to misfold, form aggregates, and deposit as unique amyloid fibrils in visceral organs. Tissue damage is caused when these light chain aggregates interact with cells and when they form large amounts of amyloid fibrils, insoluble pleated β sheet filaments in fibrils that cause end-organ dysfunction.[4] While the disease is a clonal plasma cell disease like multiple myeloma, the M-protein is often not an intact immunoglobulin and the clonal plasma cells are present at a low percentage in the bone marrow and are predominantly λ rather than κ restricted (κ-to-λ ratio is 1:4).[1, 5, 6]

Amyloidosis is a rare disease where early diagnosis and treatment are key to patient outcomes. Unfortunately, late diagnosis is still a major problem. Extracellular deposition of the fibrils ultimately results in an accumulation that disrupts normal tissue structure and function notably in the heart, kidneys, peripheral nervous system, and gastrointestinal tract with liver and soft tissues.[1] This progressive accumulation ultimately leads to organ dysfunction, organ failure, and finally death, often due to cardiac causes. The disease carries a poor prognosis which is predominantly influenced by the patient's performance status and extent of organ involvement, particularly cardiac involvement, at diagnosis. One-fourth of patients present with clinical involvement of 1 organ; however, the majority present with clinical involvement of more than one.[1, 7] Renal dysfunction is the most common clinical manifestation while liver involvement is reported but not very common. The severity of the cardiac involvement ultimately dictates the prognosis. Notably the majority of patients with AL amyloidosis die from a cardiac death, which is often sudden.[8]

The incidence of systemic AL amyloidosis has been estimated at 8.9 per million person-years in the United States, similar to that of chronic myelogenous leukemia, which translates to approximately 2,225 new cases annually in the United States (US).[2, 9] It is about one-fifth as common as multiple myeloma; however, median survival time is shorter (13.2 months from the time of diagnosis compared to 47 months for multiple myeloma).[10,

[11, 12] The natural history of AL amyloidosis includes progression to death within 2 years from diagnosis in about 80% of patients.[7]

The diagnosis of amyloidosis relies on the identification of amyloid deposits in tissues, eg, abdominal adipose aspiration, salivary glands, and organ biopsy.[13] The characterization of amyloidosis as AL type requires the demonstration of the underlying plasma cell clone. Amyloid typing is necessary and demands adequate techniques. Current practice primarily involves Congo red (CR) staining and viewing under polarized light. Combination methods such as CR plus immunoelectron microscopy, immunofluorescence, immunoperoxidase, immunohistochemistry, mass spectrometry-based methods, and genetic testing play a major role in tissue typing.[14] The importance of these techniques is to enable differentiation of the various types of systemic amyloidosis, to identify specific mutation associated with hereditary forms,[13] and to confirm the diagnosis of AL amloidosis in certain instances. Once the diagnosis of AL amyloidosis has been established, prompt initiation of treatment is required in order to inhibit growth of the malignant clone and to reduce the supply of the amyloidogenic light chains.

The death of the amyloidogenic plasma cells is the main goal of anti-AL amyloidosis therapy. Furthermore, the reduction or elimination of the amyloidogenic clone by chemotherapy has been shown to allow improvement of the function of affected organs.[3] Currently, there are no treatment modalities that specifically target the amyloid deposits. Therefore, the aim of therapy is to kill the underlying neoplastic plasma cell that produces the light chains which causes end organ dysfunction and significant toxicity for patients. Supportive measures are additionally used to preserve organ function.

The regimens used to treat subjects with systemic AL amyloidosis are based on those used in multiple myeloma therapy. However, patients with AL amyloidosis not only have a hematologic malignancy, but also have progressive organ dysfunction often of more than 1 organ. The amyloid deposits can cause symptoms that compromise the patient's clinical course by rendering them particularly susceptible to the toxic effects of chemotherapy. A rapid response is essential in order to arrest the progressive organ damage and possibly rescue its function. Hematologic and organ responses predict survival.[8, 14, 15, 16, 17, 18, 19, 20] However, given the potentially long delay in observing organ improvement, hematologic response is used as a short-term marker of treatment efficacy. Guidelines for the effective management of patients with systemic AL amyloidosis were published by the British Committee for Standards in Hematology (2004).[21] These 2004 guidelines have not been updated in recent years. According to the National Comprehensive Cancer Network

(NCCN), patients with AL amyloidosis should be treated on a clinical study as data are insufficient to identify an optimal treatment.[13]

As the approach to the treatment of multiple myeloma has evolved over the past decade, so has the approach to treatment of AL amyloidosis.[22, 23, 24] Treatments including steroids, alkylating agents, or stem cell transplant may achieve durable responses but few cures, with only about 5% of patients alive more than 10 years.[13, 25, 26, 27, 28, 29] For those considered transplant eligible, treatment generally involves high-dose melphalan followed by rescue with autologous stem cell transplantation (SCT). This approach is an aggressive treatment that can induce hematologic responses, prolonged survival, and reversal of organ disease.[30, 31] However not all patients are able to tolerate this therapy and only about one-quarter of newly diagnosed AL patients are eligible.[28] For those ineligible for SCT, other treatment options include dexamethasone plus melphalan[32] or new agents such as the immunomodulatory drugs (IMiDs; lenalidomide, thalidomide, pomolidomide).[18, 19, 33, 34, 35, 36, 37, 38, 39] Experience with IMiDs is also illustrative of the challenges encountered in the development of effective therapy. Dispenzieri, et al documented poor tolerance to high-dose (200 to 800 mg daily) thalidomide in a small phase 2 study involving 12 patients with systemic amyloidosis.[35] Within a median time on study of 72 days, 75% of patients developed progressive edema, cognitive difficulties, and constipation compared with the authors' experience with similarly treated multiple myeloma patients. In addition, 50% of patients experienced dyspnea, dizziness, and rash. The same group noted similar challenges with pomalidomide.[19] Though the hematologic response rate was 35% (complete response/partial response [CR/PR]) and 47% (CR/PR/minimal response[MR]) with organ responses seen in 2 out of 19 patients, Grades 3 to 5 adverse events (AEs) possibly attributed to on-study therapy occurred in 56% of patients, with 1 death at Day 5 from cardiac amyloidosis. Though there has been some slow improvement over the last decade, no significant improvements in early mortality have been achieved likely reflecting the limited treatment tolerability in patients with advanced AL amyloidosis, especially those with cardiac involvement.[20]

Because lack of tolerance to treatment continues to be a common feature in this disease, a better understanding of the disease and new treatment options are needed, as those currently available are inadequate for most patients. Currently, no satisfactory therapy exists for patients with AL amyloidosis that has progressed despite previous chemotherapy including stem cell transplant; therefore, the recommendation of the NCCN is to treat patients on a clinical study.[13] Investigations in proteostasis and immunoglobulin production may lead to novel strategies to treat AL amyloidosis. Pengo, et al[40, 41] have reported that differentiating

plasma cells suffer from proteotoxicity with decreased proteasome capacity even with increased protein synthesis. This imbalance of the ubiquitin proteasome system results in the accumulation of ubiquitin-conjugates and apoptotic sensitization to proteasome inhibitors.[40, 41] Amyloidosis is a protein misfolding disease and as such may be particularly sensitive to proteasome inhibition.

VELCADE (bortezomib), a selective protesome inhibitor effective in the treatment of relapsed/refractory multiple myeloma, has also been evaluated in patients with AL amyloidosis. Small retrospectivecase studies are suggestive of activity.[42, 43, 44] Most of the patients enrolled in these studies had failed previous therapies or were ineligible for SCT. Treatment with VELCADE with or without dexamethasone was characterized by rapid response and high rates of hematologic and organ responses.[42, 43] Although treatment-related mortality was uncommon in these studies, discontinuation of VELCADE due to adverse events was common.

Reece and colleagues reported on the first prospective study of single-agent VELCADE in relapsed amyloidosis.[45, 46] The primary objective of this phase 1/2 study was to determine the maximum tolerated dose (MTD) and evaluate safety. The determination of the hematologic response rate and duration of response at the MTD was a secondary objective, while assessment of organ response and overall survival were exploratory objectives. In the phase 1 portion of the study, VELCADE was generally well tolerated at doses of up to 1.6 mg/m^2 on a weekly schedule and 1.3 mg/m^2 on a twice-weekly schedule. The MTD was not reached with either dosing schedule therefore the maximum planned dose (MPD) was evaluated in the phase 2 portion of the study. A total of 70 patients were enrolled in this study, 18 at 1.6 mg/m^2 weekly, 34 at 1.3 mg/m^2 twice weekly, and 18 at lower doses during dose-escalation. Best hematologic response (CR/PR) rates were 68.8% and 66.7% respectively for the weekly and twice-weekly dosing schedules with 78% overall of responders with a durable (> 1 year) response. Responses were more rapid with the twice-weekly dosing schedule, but toxicity appeared lower with the weekly schedule. Overall, organ responses included 29% renal and 13% cardiac responses with organ response usually associated with hematologic response. Two patients had renal progression; however, no other organ disease progression was seen. The most common adverse events were fatigue, thrombocytopenia, vomiting, diarrhea, pneumonia, and syncope. Given the results of this study and activity reported in previously untreated patients,[47] 2 phase 3 studies are in development.

Currently, no satisfactory therapy exists for patients with AL amyloidosis that has progressed despite previous chemotherapy including stem cell transplant. Amyloidosis is a protein misfolding disease and may therefore be particularly sensitive proteasome inhibition. VELCADE, the first proteasome inhibitor, has been demonstrated to be safe and active in relapsed disease.[(46)] As a second generation selective reversible proteasome inhibitor with improved chemical properties, MLN9708 is a good candidate for development in AL amyloidosis. The main purpose of this clinical study is to determine the safety and activity of MLN9708 in patients with previously treated amyloidosis.

1.1.2 Study Drug

VELCADE, the first-in-class small molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc (Millennium) validated the proteasome as a therapeutic oncology target. Recognizing that proteasome inhibition is an effective anticancer therapeutic approach, Millennium has developed MLN9708, a small-molecule 20S proteasome inhibitor that has shown an increased potency in preclinical studies, which could be translated to increase clinical efficacy.

MLN9708 rapidly hydrolyzes in plasma to MLN2238, the active form that potently, reversibly, and selectively inhibits the proteasome. MLN9708 is the citrate ester of the biologically active form, MLN2238. Like VELCADE, MLN9708 is a modified dipeptidyl boronic acid derived from leucine and phenylalanine. MLN9708 was identified in a screen for a small molecule proteasome inhibitor with improved preclinical antitumor activity and pharmacokinetic properties, and would be more convenient for clinical delivery. Both VELCADE and MLN2238 are reversible proteasome inhibitors. However, MLN9708 has a shorter proteasome dissociation half-life, which allows MLN2238 to reach equilibrium with its target more rapidly than VELCADE. As a consequence of these biochemical differences, preclinical studies determined that MLN2238 could more easily move from the blood compartment to the tissue compartment, resulting in greater and more sustained pharmacodynamic effects in both bone marrow and tumor. The pharmacologic implications of this difference in binding kinetics and tissue distribution may in turn result in differences in safety and efficacy profiles in a broader range of tumors. The evidence therefore suggests that some proteasome inhibitors quickly bind to the immediately available proteasomes in the blood but then dissociate at differing rates, if at all, to the tissue.[(48)]

MLN2238 preferentially binds the β5 site of the 20S proteasome; at higher concentrations, it also inhibits the activity of the β1 and β2 sites. MLN2238 was selective for the proteasome

over a panel of several proteases (half-maximal inhibitory concentration [IC_{50}] values between 20 and100 μM), 103 kinases (IC_{50} values > 10 μM), and receptors (IC_{50} values > 10 μM). MLN2238 inhibited the cloned cardiac potassium human ether-à-go-go related gene (K^+ hERG) channel with an IC_{50} value of 60 μM. MLN2238 and VELCADE have different β5 proteasome dissociation half-lives ($t_{1/2}$), reflecting differences in their on-off binding kinetics (the β5 proteasome dissociation $t_{1/2}$ for MLN2238 and VELCADE are 18 and 110 minutes, respectively).

1.2 Preclinical Experience

1.2.1 Nonclinical Pharmacology: In Vivo Studies

Antitumor activity was observed with MLN2238 in 4 xenograft models: CWR22 (a human prostate cancer cell line), WSU-DLCL2, OCI-Ly7-7D1-luc, and PHTX-22L (3 human lymphoma cell lines). In contrast, VELCADE demonstrated weaker antitumor activity in these latter 3 lymphoma models, demonstrating that MLN2238 has improved activity in nonclinical models compared to VELCADE. MLN2238 treatment demonstrated an improved tumor pharmacodynamic response compared to VELCADE in WSU-DLCL2 human diffuse large B-cell lymphoma (DLBCL) xenografts. WSU-DLCL2 xenografts from MLN2238-treated mice displayed greater tumor 20S proteasome inhibition compared to xenografts from VELCADE-treated mice and demonstrated increased downstream biological effects, as determined by protein marker expression.

MLN2238-treated xenografts displayed higher and more sustained 20S proteasome inhibition and increased downstream biological effects as determined by Growth Arrest DNA Damage 34 (GADD34) and Activating Transcription Factor-3 (ATF-3 levels). MLN2238 demonstrated both an improved efficacy profile and pharmacodynamic response compared to VELCADE.

1.2.2 Drug Metabolism and Pharmacokinetics

The pharmacokinetic (PK) properties of MLN2238 were studied in severe combined immunodeficient mice bearing human CWR22 tumor xenografts, Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys. Because of the extensive red blood cell (RBC) partitioning of MLN2238, both blood and plasma PK parameters were determined in these studies. MLN2238 had a very low blood clearance (CL_b) and a moderate blood volume of distribution at steady-state ($V_{ss,b}$) after intravenous (IV) administration. The concentration-versus-time curve of MLN2238 displayed a distinct bi-exponential profile with a steep

initial distribution phase and a long terminal $t_{1/2}$ (> 24 hours) in all species tested. MLN2238 had higher plasma clearance (CL_p) and a larger plasma volume of distribution at steady-state ($V_{ss,p}$) than in blood, largely because of the extensive RBC partitioning.

The PK properties of MLN2238 after oral (PO) administration were studied in rats and dogs. The plasma oral bioavailability (F) was 41% in rats and nearly 100% in dogs. A clinical prototype formulation of the MLN9708 capsule demonstrated that MLN2238 had excellent oral F and an excellent absorption profile in dogs. In addition, after PO administration, interindividual variability (as measured by percent coefficient of variation) in maximum plasma concentration (C_{max}) and area under the plasma concentration versus time curve zero to 24 hours ($AUC_{0\text{-}24hr}$) was low to moderate, similar to that after IV administration. The terminal $t_{1/2}$ after PO administration was also similar to that after IV administration.

MLN2238 is predicted to have very low CL_b (0.0045 L/hr/kg) and a moderate $V_{ss,b}$ (0.79 L/kg) with a long terminal $t_{1/2}$ (> 24 hours) in humans. The human efficacious IV dose of MLN2238 is predicted to be 2.0 mg/m^2 (0.054 mg/kg) twice weekly. The projected PO efficacious dose is between 2 and 5 mg/m^2 twice weekly. It is anticipated that the plasma AUC at the PO efficacious dose will be similar to that at the IV efficacious dose ($AUC_{0\text{-}24hr}$ = 143 hr × ng/mL) and that the systemic effects are probably driven by plasma AUC.

Metabolism appears to be the major route of elimination for MLN2238 and urinary excretion of the parent drug is negligible (< 3% of dose). In vitro studies indicate that MLN2238 is metabolized by multiple cytochrome P_{450s} (CYPs) and nonCYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human cytochrome P450 (CYP) isozymes was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). All metabolites observed in the human liver microsome studies were also found in the rat and dog, supporting the rat and dog as the species to be used for toxicology studies. MLN2238 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4 (IC_{50} > 30 μM, estimated K_i > 15 μM) nor a time-dependent inhibitor of CYP3A4/5 (up to 30 μM). The potential for MLN9708 treatment to produce drug-drug interactions (DDI) via CYP inhibition is inferred to be low. However, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor because of the potential for first-pass metabolism when MLN2238 is administered via the PO route, and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of MLN2238 in human liver microsomes. To ensure patient safety and minimize PK variability in this first-in-human

investigation of the PO formulation of MLN9708, strong inhibitors of CYPs 3A and 1A2 and strong CYP3A inducers are identified as excluded concomitant medications.

MLN2238 may be a weak substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN2238 is not an inhibitor of P-gp, BCRP, and MRP2 (IC_{50} > 100 μM). The potential for DDI with substrates or inhibitors of P-gp, BCRP, and MRP2 is therefore inferred to be low.

1.2.3 In Vivo Toxicology in Rats and Dogs

Compromise of gastrointestinal (GI) and lymphoid systems led to dose-limiting toxicity in both rats and dogs. Additionally, at doses below those associated with dose-limiting toxicity, alterations in leukocyte and coagulation parameters consistent with an inflammatory response were seen in both rats and dogs. The toxicologic effects seen in rats in the Good Laboratory Practice (GLP)-compliant, 2-cycle, PO toxicology study (inhibition of erythropoiesis, thrombocytopenia, leukocyte and coagulation profile consistent with an inflammatory response, intestinal mucosal thickening and inflammation, thymus and lymph node lymphoid depletion, adrenal gland vacuolation) were largely consistent with the toxicologic effects seen in rats in the GLP-compliant, 2 cycle, IV toxicology study, for which the dosing schedule was identical. Differences of note between the IV and PO studies in rats included a trend towards leukocytosis in the PO study versus a trend toward leukopenia (with corresponding bone marrow hypocellularity) in the IV study, as well as histologic findings in the peripheral nervous system in the IV study, but not in the PO study. In the rat IV study, leukocytosis was seen before leukopenia. Additionally, in early-death rats in the PO study, bone marrow hypocellularity was seen; had the rats survived, this would likely have resulted in peripheral cytopenias. Higher exposures were achieved in the IV study compared to the PO study, and differences seen in peripheral white blood cell (WBC) counts and bone marrow hypocellularity between the 2 studies may reflect differences in exposures. Similarly, the decreased exposures achieved after PO versus IV administration may account for the lack of peripheral nervous system effects seen in the PO study. The toxicologic effects seen in both of these studies are qualitatively similar to what was previously observed in rodents treated with VELCADE.[49]

Although the GI and lymphoid system compromise, as well as the leukocyte and coagulation profile consistent with an inflammatory response, was consistent between rats and dogs, there were differences in the toxicologic effects between these 2 species. Differences

included a much more profound effect on lymphoid tissues at dose-limiting toxicity in dogs as compared to rats, as well as toxicologic effects seen in the peripheral nervous system of dogs (peripheral ganglia neuronal degeneration with secondary axonal degeneration), but not of rats. In dogs, neuronal degeneration in peripheral autonomic ganglia likely contributed to functional GI effects. These differences are consistent with the differences observed previously in GLP-compliant studies in dogs and rats after IV administration of MLN9708. Additionally, there were no significant findings at tolerated exposures in dogs observed after PO administration that were not seen after IV administration, and similar exposures were tolerated regardless of the route of administration. All of the effects seen in both dogs and rats at tolerated doses were reversible or reversing.

The potential risks identified from nonclinical studies in dogs and rats include:

- GI toxicity that could result in nausea, vomiting, diarrhea, dehydration, electrolyte imbalance, bleeding, bowel obstruction including ileus and intussusception, and sepsis.
- Reduced blood counts manifest as thrombocytopenia, neutropenia, and anemia. Reticulocytopenia was described in animals and may be associated with anemia. Reductions in blood counts may predispose to an increased susceptibility to infection, bleeding, and anemia.
- Peripheral nerve ganglia effects that may be associated with peripheral neuropathy that includes pain, burning sensation, and numbness. Autonomic and motor neuropathy may be observed, as both have been reported for VELCADE.
- Lymphoid cell depletion that may be associated with increased risk of infection, including re-activation of herpes zoster.
- Acute phase response that may result in fever and metabolic changes.

Detailed information regarding the nonclinical pharmacology and toxicology of MLN9708 may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

MLN9708 is a boronic acid proteasome inhibitor similar to VELCADE. Clinical studies with VELCADE have yielded a detailed understanding of its safety profile. For details, refer to the package insert for VELCADE.[50] MLN9708 is in the early stages of clinical

investigations in humans with safety, tolerability, PK, pharmacodynamics, electrocardiogram (ECG) parameters, and disease response assessed in each study. MLN9708 is the first investigational proteasome inhibitor with substantial oral bioavailability in patients with MM.

As of 24 September 2010, 112 patients have been treated with single-agent MLN9708 across 4 phase 1 studies (C16001, IV administration twice weekly in adult patients with advanced nonhematologic malignancies, n = 67; C16002, IV administration weekly in adult patients with advanced lymphoma, n = 11; C16003 and C16004 PO administration twice weekly and weekly, respectively, in adult patients with relapse or refractory multiple myeloma, n = 19 and 15, respectively). Regardless of the route of administration in the twice-weekly dosing schedule, MLN9708 is given on Days 1, 4, 8, and 11 of a 21-day cycle and, in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle.

In the 2 studies investigating PO MLN9708 in relapsed or refractory multiple myeloma, a total of 34 patients have been treated thus far at doses of 0.24 mg/m^2 to 2.23 mg/m^2 twice a week (C16003) and 0.24 mg/m^2 to 1.68 mg/m^2 weekly (C16004). To date in study C16003 (PO, twice weekly), 6 patients have experienced treatment-related AE ≥ Grade 3 (thrombocytopenia [2 pts], neutropenia [2 pts], anemia [1 pt], rash [1 pt- DLT], oral candidiasis [1 pt], and 1 patient that experienced nausea, vomiting, abdominal and chest pain [non-cardiac] for which they were hospitalized), otherwise there have not been any drug-related serious adverse events (SAEs). In study C16004 (PO, weekly), there have not been any treatment-related AEs ≥ Grade 3 or any drug-related SAEs. In the study investigating IV MLN9708 in advanced lymphoma (C16002; IV weekly), a total of 11 patients have been treated at doses ranging from 0.125 mg/m^2 to 1.76 mg/m^2 weekly with 2 treatment-related AEs ≥ Grade 3 occurring in ≥ 2 patients at any point during the course of therapy: 1 each Grade 3 neutropenia and Grade 4 neutropenia that lasted more than 7 days (meeting the definition of a dose-limiting toxicity [DLT]), and 2 Grade 3 thrombocytopenia with no drug-related SAEs.

In study C16001(IV, twice weekly), 67 evaluable patients with advanced nonhematologic malignancies have been treated across 7 dose levels, ranging from 0.125 mg/m^2 to 2.34 mg/m^2 twice weekly. At the 1.0-mg/m^2 dose level, 1 out of 6 patients experienced a DLT (transient Grade 3 rash); no drug-related SAEs reported. No additional DLTs were reported as the dose was escalated up to 1.76 mg/m^2. At the 2.34-mg/m^2 dose level, 3 out of 3 patients were admitted to the hospital with DLTs (1 reversible Grade 3 acute renal failure, 2 reversible Grade 4 thrombocytopenia). All 3 patients recovered; 1 patient, who had

experienced thrombocytopenia, continued on study at a reduced dose of MLN9708 for an additional 3 cycles before disease progression. Given these AEs, the MTD of IV MLN9708 administered twice weekly is determined to be 1.76 mg/m^2.

In contrast to the AEs experienced by the patients at the highest dose administered in C16001, 50 patients (6 in the dose escalation phase, 44 from the dose expansion phase) have been treated at the MTD of 1.76 mg/m^2. In these patients fatigue, nausea, vomiting, diarrhea, anemia, thrombocytopenia, rash, constipation, fever, abdominal pain, back pain, cough, chills, headache, and dyspnea are the most common treatment-emergent AEs. One patient treated at the MTD had experienced renal toxicity, 1 patient experienced Grade 3 transient peripheral sensory neuropathy during Cycle 2, and 1 Grade 3 peripheral neuropathy at the end of treatment after completion of 3 cycles. Eleven SAEs have been reported in the 1.76-mg/m^2 dose cohort where the investigators considered MLN9708, as well as alternative etiologies, as a possible cause (1 each Grade 3 reversible: depressed level of consciousness, pneumonitis, pneumonia, rash, and ileus; 2 each Grade 3 reversible: fatigue and dehydration; 1 Grade 2 shingles, 1 Grade 4 elevated creatinine).

During enrollment in the expansion cohort of Study C16001 (dosing at 1.76 mg/m^2), 1 patient (among 44 patients treated as of 24 September 2010) has experienced acute renal failure (NCI CTCAE [version 3.0] Grade 4 increased creatinine). Both cases of acute renal failure reported to date (the other patient was treated at the 2.34 mg/m^2 dose level) share the following features: (1) a pre-existing kidney condition (status post nephrectomy due to kidney cancer and prior hydronephrosis due to disease progression); (2) prior exposure to other antineoplastic drugs associated with nephrotoxic potential; (3) diarrhea and/or poor oral intake; (4) use of nonsteroidal antiinflammatory drugs during the 24 to 48 hours before the onset of the AE; (5) the event occurred after a total of 4 doses of study drug had been administered (1 patient received all 4 doses within Cycle 1, while the second patient received them over the course of 2 treatment cycles); and (6) concomitant with event, the patient experienced thrombocytopenia.

One patient in Study C16001 received a dose of MLN9708 higher than was planned per protocol. The patient's dose was calculated based on pounds when the reported weight was actually in kilograms, this resulted in the patient twice receiving a dose of MLN9708 approximately 46% higher than was intended per the protocol. The patient experienced Grade 4 thrombocytopenia (nadir 22 k/uL), some liver function elevations, but no other issues including no elevation in creatinine. All laboratory abnormalities resolved 8 days after the overdose.

Additional trials are planned or recently started enrollment, each of which will use the oral formulation of MLN9708 (Study C16005, PO weekly MLN9708 added to lenalidomide and dexamethasone in a 28 day cycle in patients with NDMM; Study C16006, phase 1/2, PO MLN9708 added to melphalan and prednisone in patients with newly diagnosed multiple myeloma [NDMM]; Study C16008, PO twice weekly administration in combination with lenalidomide and low-dose dexamethasone in adult patients with NDMM requiring systemic treatment every 21 days; and Study C16009, phase 1 study of oral MLN9708 to assess drug-drug interaction with ketoconazole, relative bioavailability, food effect, and safety and tolerability in patients with advanced nonhematologic malignancies or lymphoma).

The emerging safety profile indicates that MLN9708 is generally well tolerated with manageable and reversible treatment-emergent adverse events (TEAEs) or adverse reactions. The most common treatment-related adverse drug reactions reported with MLN9708 use pooled from the 4 phase 1 early human studies (including both IV and oral formulations) include thrombocytopenia and maculopapular rash, with or without pruritus. Other treatment-emergent side effects reported across these studies, which may have been due to either the patient's disease of MLN9708 include nausea, vomiting, diarrhea, constipation, dehydration, anorexia, fatigue, anemia, fever, abdominal pain, peripheral edema, cough, headache, and insomnia. The most frequent (> 10%) TEAEs of any grade reported across the 2 phase 1 studies using the oral formulation, C16003 and C16004, irrespective of causality to MLN9708, include fatigue (44%), diarrhea (26%), nausea and anemia (19% each), cough (15%), and dyspnea (11%). Please refer to the IB and Safety Management Attachment for further details. The most frequent AEs were anticipated based on preclinical data and previous experience with VELCADE and are noted in the current IB, the Safety Management Attachment, and the informed consent documents. While the potential toxicities may be severe, they are managed by appropriate clinical monitoring and standard medical interventions.

While safety, PK and pharmacodynamic objectives are the primary focus of the 4 phase 1 studies currently enrolling patients, preliminary assessments of disease response are also being evaluated. The most common preliminary observation of response in these heavily-pretreated patients (n = 112 as of 24 September 2010) is stabilization of the underlying disease: 6 patients with various nonhematologic malignancies in Study C16001 which uses the IV formulation, including reported tumor reductions of 18% and 22% in 2 patients with renal cell carcinoma; 2 patients with lymphoma in Study C16002 which uses the IV formulation, including 1 patient with a reported 44% reduction in tumor; and 2 patients with

relapsed/refractory MM in Study C16004 dosing oral MLN9708 weekly. In patients with relapsed or refractory MM in Study C16003, oral dosing twice-weekly, there has been 1 PR in a patient with relapsed disease after VELCADE treatment and 6 patients reported to have stable disease. The MTD has been established only in Study C16001 with dose-escalation continuing in the 3 other studies. Based on the proven utility of VELCADE in the treatment of MM and MCL and MLN9708's increased tissue distribution as well as activity in several xenografts models, it is anticipated that MLN9708 directed against the same components of the ubiquitin-proteasome system (UPS) will prove efficacious in the treatment of similar if not additional malignancies.

1.3.1 Pharmacokinetics and Pharmacodynamics

MLN9708 completely hydrolyzes to the boronic acid MLN2238 in aqueous solutions. MLN2238 is the only form of MLN9708 measurable in plasma or urine.

Based on preliminary clinical data from the first-in-human study of MLN9708 (C16001), following IV administration of MLN9708, MLN 2238 shows multi-exponential plasma disposition, characterized by a rapid initial disposition phase ($t_{1/2}$ of < 0.25 hours), 1 or more intermediate disposition phases, and a slow terminal disposition phase ($t_{1/2}$ of > 4 days). The Day 1 and Day 11 extrapolated immediate post-IV bolus plasma concentration of MLN2238 (C0) and AUC show proportional increases with increasing dose. There is accumulation of MLN2238 with multiple dosing; AUC_{tau} following the Day 11 dose of MLN9708 is an approximately 4-fold accumulation of MLN9708 by Day 11 on the biweekly schedule.

The pharmacodynamic effect being evaluated in the development of MLN9708 is red cell proteasome inhibition as measured by whole blood 20S proteasome activity. Based on preliminary clinical data from study C16001, following IV administration of MLN9708, maximum whole blood 20S proteasome inhibition occurs at the earliest sampled time points (0.8 or 0.25 hours) and increases with increasing dose over the dose range studied. Inhibition is short-lived (approximately 4 hours) following the Day 1 dose but is prolonged following the Day 11 dose.

Further details on these studies are provided in the IB.

1.4 Study Rationale

Amyloidosis is a protein conformational disease due to a clonal plasma cell dyscrasia that is related to multiple myeloma.[45] Aggregation of normally soluble proteins into insoluble ß-

sheet fibrils are deposited into target tissues causing progressive organ dysfunction that leads to organ failure and death. The neoplastic plasma cells that cause amyloidosis suffer from proteotoxicity resulting in an imbalance in the ubiquitin proteasome system and thus may be particular sensitive to proteasome inhibition.[(40)] VELCADE has validated the proteasome as a therapeutic target for hematologic malignancies, where it is now indicated in the treatment of multiple myeloma and mantle cell lymphoma. Recognizing that proteasome inhibition is an effective anticancer therapeutic approach, Millennium has developed MLN9708, a small-molecule, orally bioavailable 20S proteasome inhibitor, with the aim of improving the pharmacology of the agent thereby building on the efficacy seen with VELCADE, while improving drug administration. This study is proposed based on the results of VELCADE in previously treated amyloidosis[(51)] and the urgent need for better treatment options for this rare disease, especially in the relapsed setting where no standard treatment exists.

The purpose of this study is to determine the safety, MTD, and recommended phase 2 dose (RP2D) of MLN9708 treatment in patients with AL amyloidosis who have relapsed or experienced progressive disease (PD) despite prior therapy. The study will also include hematologic and organ efficacy assessments.

Given that AL amyloidosis can present in a variety of organs yet the most objective organ response criteria involve AL amyloidosis that affects the kidney and heart, patients eligible for this study must have amyloid involvement of at least one of those organs. Patients may present with amyloidosis involvement of additional organ systems, for example liver/ gastrointestinal and autonomic/ peripheral nervous system, but they must also have either kidney and/or heart involvement. However, patients with the poorest prognosis of cardiac status are excluded in order to ensure a comprehensive characterization of the safety profile and activity of MLN9708 in AL amyloidosis.

Further, because no approved therapy exists for patients with AL amyloidosis, experts, including the NCCN,[(13)] recommend treatment of patients on clinical studies. At relapse, given the limited treatment options, patients seek subsequent treatment even if it means exposure to an agent from the same drug class. MLN9708 is structurally similar to the first in class proteasome inhibitor VELCADE, which in some parts of the world is used to treat AL amyloidosis. It is unlikely that there will be significant differences in safety, based on the emerging safety data from ongoing Phase 1 studies in patients with relapsed or refractory multiple myeloma who have been previously treated with proteasome inhibitors, however there may be differences in activity. Therefore, patients are eligible regardless of prior

exposure to proteasome inhibition therapy in the dose escalation phase. Once the MTD/RP2D has been established, separate enrollment will begin for 2 expansion cohorts, (one for patients that are proteasome inhibitor-naïve and one for patients who have been exposed to proteasome-inhibitor therapy) in order to better understand the potential activity of MLN9708 in this patient population.

1.5 Rationale MLN9708 Dose and Schedule Selection

The schedule of MLN9708 is based on results of single-agent VELCADE from Reece, et al[51] where the hematologic response rate, duration of response, and organ response rate were similar between the weekly and twice-weekly schedules, but the toxicity appeared lower with the weekly dosing. The estimated safe starting dose of MLN9708 will be selected from the dose-escalation portion of the C16004 study, a phase 1 study of weekly dosing in patients with relapsed and refractory multiple myeloma. The starting dose will be at least 1 dose level below the C16004 MTD if it has been reached by the time this study starts, and if not, then a dose level completed without reported DLTs when MLN9708 is administered weekly as a single agent (Section 1.3).

A population PK analysis was performed for MLN9708 to assess the feasibility of switching from body surface area (BSA)-based dosing to flat dosing. A population PK model was built using nonlinear mixed effects modeling in NONMEM VII software compiled with the Intel Fortran 9.2 compiler. Data from both the twice weekly and once weekly IV dosing regimens were used in the analysis (N = 42). Population PK analysis showed that MLN9708 PK can be well described by a 3-compartment model with linear elimination. Race, sex, BSA, and/or body weight do not appear to significantly affect clearance (CL) and volume of distribution (V_1) in the central compartment. Clearance and volume of distribution in the central compartment are the PK parameters that will affect AUC and C_{max}, respectively. CL and V_1 are primary parameters that are independent of the route of administration of drug. Therefore, BSA is not expected to affect C_{max} or AUC after oral dosing, and thus flat dosing is appropriate for both oral and IV routes of administration.

1.6 Rationale for Collection of PK and Pharmacodynamic Samples

A limited number of PK and pharmacodynamic samples will be collected so that the PK and pharmacodynamics of MLN9708 can be characterized in this population. This evaluation is being undertaken to assess if chronic organ injury caused by amyloidosis affects the absorption or systemic disposition of MLN9708 and to assess if the disease state alters the whole blood pharmacodynamic effect of MN9708 treatment.

1.7 Rationale for Tumor Biomarker Assessment

CCI

1.8 Potential Risks and Benefits

MLN9708 is a modified dipeptide boronic acid proteasome inhibitor similar to VELCADE, which has a known safety profile. The most frequent AEs reported to date in the ongoing MLN9708 phase 1 studies were anticipated based on preclinical data and previous experience with VELCADE, and are noted in the IB, the Safety Management Attachment, and the informed consent documents. However, it is possible that MLN9708 will have toxicities that were not previously observed in or predicted from such sources. Patients will be monitored closely for anticipated toxicities.

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To determine the safety, tolerability, and MTD of oral MLN9708 administered weekly in patients with previously treated relapsed/refractory AL amyloidosis
- To determine the RP2D of oral MLN9708 administered weekly

2.2 Secondary Objectives

- To characterize the plasma PK and whole blood pharmacodynamic effect of MLN9708 in this patient population
- To assess the rate of organ response and organ improvement according to standardized criteria
- To assess overall hematologic response rate (complete response [CR], very good partial response [VGPR], and partial response [PR])
- To assess time to hematologic and organ response, respectively
- To assess duration of hematologic and organ response, respectively
- To determine time to hematologic and organ disease progression, respectively
- To assess hematologic and organ disease progression free survival (PFS)
- To assess overall survival including 1-year survival rate

2.3 Exploratory Objectives

CCI

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoints include:

- AEs, SAEs, assessments of clinical laboratory values, and neurotoxicity grading of oral MLN9708 administered once weekly in a 28-day cycle
- MTD and RP2D of oral MLN9708 based on both toxicity and efficacy outcomes as above

3.2 Secondary Endpoints

The secondary endpoints include:

- Single- (MTD cohort) and multiple-dose plasma PK after oral MLN9708
- Whole blood 20S proteasome activity profile and inhibition parameters of multiple-dose oral MLN9708
- Organ response and organ improvement according to standardized criteria
- Overall hematologic CR + VGPR + PR
- Time to organ or hematologic response, measured as the time from the first dose of MLN9708 to the date of first documentation of a confirmed organ or hematologic response, respectively
- Duration of organ or hematologic response, measured as the time from the date of first documentation of a confirmed organ or hematologic response to the date of confirmed organ or hematologic disease progression, respectively
- Time to organ and hematologic progression, measured as the time from the date of the first dose of MLN9708 to the date of first documented organ or hematologic disease progression
- Organ and hematologic disease PFS, defined as the time from the date of the first dose of MLN9708 to the date of confirmed organ or hematologic disease progression or death, respectively.

- One-year survival, defined as the patient survival probability at 1 year after the date of first dose of MLN9708

3.3 Exploratory Endpoints

4. STUDY DESIGN

4.1 Overview of Study Design

This is a phase 1, open-label, multicenter clinical study using the oral formulation of MLN9708 in patients with previously treated systemic AL amyloidosis who require further therapy. As many as 30 patients will be enrolled in the dose-escalation portion of the study, and as many as 20 patients will be enrolled in the expansion cohorts. Overall, as many as 50 patients will be enrolled.

The dose-escalation portion of the study will be aimed at determining the safety profile and the MTD/RP2D of MLN9708 administered weekly in patients with previously treated AL amyloidosis. Patients will receive escalating doses of MLN9708 PO on Days 1, 8, and 15 in a 28-day cycle in the absence of disease progression or unacceptable toxicity.

Once the MTD/RP2D has been established, 2 expansion cohorts of patients with relapsed or refractory amyloidosis, including approximately 10 proteasome inhibitor-naïve patients and approximately 16 proteasome inhibitor-exposed patients, will be treated at the MTD/RP2D to more fully characterize the safety, tolerability, and efficacy of MLN9708, and the PK and

pharmacodynamics of MLN9708 in this patient population. As many as 30 patients will be enrolled in the dose-escalation portion of the study, and as many as 20 additional patients (26 in total, including 6 patients from the dose-escalation portion) will be enrolled in the expansion cohorts.

The estimated safe starting dose of MLN9708 will be selected from the dose-escalation portion of the C16004 study, an ongoing phase 1 study of weekly dosing in patients with relapsed and refractory multiple myeloma. The starting dose will be at least 1 dose level below the C16004 MTD if it has been reached by the time this study starts, and if not, then a dose level completed without documented DLTs.

A 3 + 3 dose-escalation scheme will be implemented and dose intervals will follow those outlined in Section 6.4. Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment in the phase 1 portion will necessarily influence decisions regarding dose-escalation, expansion of a dose level, or evaluation of intermediate dose levels. In the context of emerging clinical data of single-agent MLN9708, dose-escalation of MLN9708 will continue until the MTD has been identified or a maximum planned dose (MPD) is determined to be safe. Based on experience with other drugs in this condition, it is considered unlikely that patients with systemic AL amyloidosis will tolerate doses higher than those tolerated in other diseases, such as multiple myeloma. Therefore, the maximum dose in patients with systemic AL amyloidosis may be the MTD as recommended from the phase 1 single-agent study of weekly MLN9708 in relapsed/refractory multiple myeloma (C16004). For treatment Cycle 2 and beyond, doses of MLN9708 may be held or reduced in an attempt to manage toxicity according to the guidelines outlined in Section 6.6.

More conservative dose-escalation, evaluation of alternative dosing, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics of MLN9708.

Treatment repeats every 28 days for 3 cycles. If there is no hematologic response (PR, VGPR, or CR) after completion of 3 cycles of single-agent MLN9708, dexamethasone will be added at the initially recommended dose of 40 mg on Days 1 to 4 of every cycle (d1-4 q28days), beginning in Cycle 4. For patients with fluid retention > 3% of body weight despite optimal diuretic therapy, a starting dose of dexamethasone 20 mg should be considered. The patient's response status will be reassessed after 3 additional cycles; if there

is no hematologic response at that time, the patient will be removed from treatment and followed for survival.

If there is response with MLN9708 alone or dexamethasone and MLN9708, the patient may continue on study for up to 12 cycles of treatment in the absence of PD. Study treatment beyond 12 cycles is allowed only if clinical benefit is clearly indicated after a discussion between the Millennium clinician and the investigator treating the patient.

Radiological evaluations and serial blood/urine samples will be employed to assess the status of the patient's amyloidosis. An evaluation of disease response using standardized criteria [53, 54] will be performed after each cycle during treatment and then at regular intervals during follow-up.

If patients are removed from treatment for unacceptable toxicity or reasons other than PD, they will continue in PFS follow-up until documented disease progression or the initiation of subsequent antineoplastic therapy. Once a patient experiences PD or starts subsequent antineoplastic therapy, they will proceed to the OS follow-up phase.

4.2 Number of Patients

As many as 50 patients will be enrolled in this study. As many as 30 patients will be enrolled in the dose-escalation portion of the study. Because approximately 6 patients in the dose-escalation part of the study will be included in the expansion cohort, approximately 20 patients will be enrolled in the expansion part of this study after taking the dropout rate into consideration. Patients will be enrolled from approximately 10 centers in North America and Europe. Enrollment is defined as the time the patient receives the first dose of any study drug.

4.3 Duration of Study

The duration of enrollment will be approximately 24 months.

Patients who have a response to treatment may remain on treatment for a maximum of 12 cycles or until the occurrence of PD or unacceptable toxicity, whichever occurs first. Patients who stop treatment for any reason other than disease progression will continue in PFS follow-up and be seen every 6 weeks until documented disease progression. After disease progression, all patients will continue to the OS follow-up part of the study and will be contacted every 12 weeks.

Delayed treatment-related AEs will be followed for 30 days after last dose of study drug or until initiation of subsequent antineoplastic therapy. The analyses for the clinical study report will be conducted after 75% of patients have PD or 12 months after last patient is enrolled, whichever occurs first in the study.

It is anticipated that this study will last for approximately 84 months. The duration of follow-up for overall survival will be 60 months after the last patient enters the study. Treatment may be continued in this study or in a MLN9708 rollover study, if and when such a study is made available, upon request by the investigator and agreement by the project clinician.

5. STUDY POPULATION

Adult patients with biopsy-proven systemic AL amyloidosis with relapsed or progressive disease despite prior therapy will be enrolled.

5.1 Inclusion Criteria

1. Male or female patients 18 years or older.
2. Histologic diagnosis of AL amyloidosis, confirmed by pathology-positive Congo red stain with green birefringence on polarized light microscopy, with evidence of measurable clonal disease according to standardized criteria[54, 55, 56] that requires active treatment (see Section 15.2 for amyloid typing).
3. Patients will have a measurable disease as defined by serum differential free light chain concentration (dFLC, difference between amyloid forming and nonamyloid forming free light chain [FLC]) ≥ 40 mg/L.
4. Percentage of plasma cells < 30% in the bone marrow aspirate and biopsy.
5. Patients must have objective, measurable major organ (heart or kidney) involvement.
   a. renal: albuminuria higher than 0.5 g/day in 24-hour urine analysis.
   b. cardiac: involvement is defined as the presence of a mean left ventricular wall thickness on echocardiogram more than 12 mm in the absence of a history of hypertension or valvular heart disease, or unexplained low voltage (< 0.5 mV) on electrocardiogram; or NT-proBNP > 332 ng/L in the absence of renal failure (estimated glomerular filtration rate [eGFR] < 45 mL/min/1.73 m^2).

In addition, patients can also have amyloidosis organ involvement in such organ systems as liver/GI tract, peripheral nerves, or soft tissue. Skin purpura, carpal tunnel syndrome, or the presence of vascular amyloid on a bone marrow biopsy alone are not sufficient to meet criteria for "symptomatic organ involvement". Patient may present with **any** of the following amyloid-related organ involvement as defined below:

a. hepatic: hepatomegaly on physical examination with alkaline phosphatase > 1.5 × the upper limit of normal (ULN).

b. gastrointestinal: direct biopsy verification of amyloid involvement with symptoms such as gastrointestinal bleeding (confirmed by tissue biopsy) or diarrhea (at least 4 stools per day). A positive GI biopsy change is not sufficient.

c. autonomic or peripheral neuropathy: based on clinical history, autonomic dysfunction with orthostasis, symptoms of nausea or dysgeusia, gastric atony by gastric emptying scan, diarrhea or constipation, or abnormal sensory and/or motor findings on neurologic examination.

d. soft tissue and lymphatic: based on physical examination findings (macroglossia, shoulder pad sign, raccoon eyes, carpal tunnel syndrome, synovial enlargement, or firm enlarged lymph nodes) or biopsy.

6. AL Amyloidosis Risk stage I or II disease.

   Staging system defined by: NT-proBNP cut off of < 332 pg/mL and troponin T cut-off of 0.035 ng/mL as thresholds: Stage I, both under threshold; Stage II, either troponin or NT-proBNP [but not both] over threshold; if troponin T not available at local institution, troponin I may be used, but threshold is < 0.1 ng/mL.[57]

7. Must be relapsed or refractory after at least 1 prior therapy for AL amyloidosis and, in the investigator's opinion, requires further treatment.

   NOTE: If a patient has received a transplant as his/her first therapy, he/she must be at least 3 months posttransplantation and recovered from the side effects of the stem cell transplant.

   Any patient who was not a candidate for high-dose therapy and was unable to tolerate an alkylating agent plus a corticosteroid (eg, melphalan plus prednisone) or patients who are intolerant to an alternative prior therapy after receiving at least 1 cycle of such therapy because of severe adverse events

(eg, hypersensitivity reaction) also can be considered for enrollment after discussion with the Millennium clinician.

8. Patients must have an Eastern Cooperative Oncology Group (ECOG) status of 0 to 2 (see Section15.3)
9. Clinical laboratory values as specified below within 3 days before the first dose of study drug (unless otherwise noted):
    a. echocardiographic ejection fraction ≥ 40% within 28 days before the first dose of study drug.
    b. platelet count ≥ 75×10^9/L.
    c. neutrophil count ≥ 1.0×10^9/L.
    d. total bilirubin ≤ 1.5 × ULN.
    e. alkaline phosphatase ≤ 5 × ULN.
    f. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN.
    g. eGFR ≥ 45 mL/min/1.73 m^2 (see Section 15.1 for the Equation to Estimate Glomerular Filtration Rates).
10. Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug, or agree to completely abstain from heterosexual intercourse.
11. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
    - Agree to completely abstain from heterosexual intercourse.
12. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

5.2 Exclusion Criteria

1. Known allergy to any of the study medications, their analogues, or excipients in the various formulations.
2. Treatment with any investigational products within 28 days before the first dose of study drug.
3. Requirement for other concomitant chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered to be investigational.
4. Failure to have fully recovered (ie, ≤ Grade 1 toxicity) from the effects of prior chemotherapy regardless of the interval since last treatment.
5. Cardiac system:
    a. QTc > 470 milliseconds (msec) on a 12 lead ECG obtained during the Screening period. If a machine reading is above this value, the ECG should be reviewed by a qualified reader and confirmed on a subsequent ECG.
    b. AL Amyloidosis Risk Stage III disease Staging defined by: NT-proBNP cut off of < 332 pg/mL and troponin T cut-off of 0.035 ng/mL as thresholds: stage III, both over threshold; if troponin T not available at local institution, troponin I may be used, but threshold is < 0.1 ng/mL[57]
    c. New York Heart Association (NYHA) classification III or IV. See Section 15.4 for criteria.
    d. Enzyme-documented myocardial infarction within 6 months before enrollment.
    e. Chronic atrial fibrillation.
    f. Grade 2 or 3 atrioventricular (AV) block (Mobitz, Type I permitted).
    g. Sustained (> 30 seconds) ventricular tachycardia, more than 1 episode of nonsustained ventricular tachycardia (defined as 3 consecutive ventricular beats), or frequent (> 20/24 hours) ventricular pairs, detected by 24-hour ambulatory electrocardiographic monitoring.
    h. Supine systolic blood pressure < 90 mmHg, or symptomatic orthostatic hypotension, or a decrease in systolic blood pressure on standing of > 20 mm Hg in spite of being treated for orthostatic hypotension.
    i. History of a bleeding diathesis or currently receiving treatment with warfarin. Patients are allowed to take aspirin.

7. GI system:
    a. Severe diarrhea (≥ Grade 3) not controllable with medication (such as octreotide) or requires administration of total parenteral nutrition.
    b. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of study drug, including difficulty swallowing.
8. Neurologic/ Social system:
    a. Patients with ≥ Grade 2 peripheral neuropathy or painful peripheral neuropathy on clinical examination will be excluded.
    b. Previous or ongoing psychiatric illness and/or social situations that would limit compliance with study requirements.
9. Systemic infections:
    a. Known to be human immunodeficiency virus (HIV)-positive.
    b. Known to be hepatitis B surface antigen-positive or has known or suspected active hepatitis C infection.
    c. Uncontrolled infection requiring systemic antibiotics.
10. Other malignant disease/s:
    a. Clinically overt multiple myeloma (bone marrow plasma cells ≥ 30%), and at least 1 of the following: bone lesions, anemia (< 100 g/L), and hypercalcemia.
    b. Patients with amyloidosis due to mutations of the transthyretin gene (see Section 15.2).
    c. Patients with non-AL amyloidosis (see Section 15.2).
    d. Presence of other active malignancy with the exception of nonmelanoma skin cancer, cervical cancer, treated early-stage prostate cancer provided that prostate-specific antigen is within normal limit, or any completely resected carcinoma in situ.
11. Female patients who are lactating or pregnant.
12. Major surgery within 14 days before the first dose of study drug.
13. Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers

(rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before the first dose of study treatment.

14. Any other serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

6. DESCRIPTION OF TREATMENT

6.1 Study Drug

The study drug will be administered at the Amyloidosis Research and Treatment Center. The treatment schedule for each patient will be provided to the Intensive Care Department at least 1 week before commencing each treatment cycle. The Intensive Care Unit will grant availability on the days of MLN9708 administration, in the event that any adverse events occur that require emergency or intensive care.

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity as necessary and doses of MLN9708 should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions and adjustments of MLN9708 dose. All doses must be taken as outlined in the Schedule of Events. No doses should be missed or delayed during Cycle 1 due to patient scheduling. Following agreement between the investigator and the sponsor, eligible patients may take study drug at home as directed.

Refer to Study Manual for additional instructions regarding study drug administration.

MLN9708 Administration

The study drug should be taken on an empty stomach, at least 1 hour before or no sooner than 2 hours after a meal. The capsules should not be chewed, broken, or opened for administration. Each capsule should be swallowed separately with approximately 240 mL (ie, 8 oz) total of water with the full dose. MLN9708 will be given as a single daily oral dose. The dose will be assigned based on the dose-escalation methodology outlined in Table 6-1. Administration of the capsules may be guided by the dosing tables included in the pharmacy manual.

The prescribed administration of MLN9708 doses in this study is weekly x 3 followed by 1 week without MLN9708 in a 28-day cycle. Missed doses can be taken as soon as the patient remembers as long as the next scheduled dose is 70-72 hours or more away. Patients who vomit after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose.

Dexamethasone Administration

If a patient does not have a response after 3 cycles of MLN9708 treatment, dexamethasone will be added. Dexamethasone will be given as a single, oral dose of 40 mg/day on Days 1 through 4 of a 28-day cycle beginning with Cycle 4. For patients with fluid retention > 3% of body weight despite optimal diuretic therapy a starting dose of dexamethasone 20 mg should be considered.

Dexamethasone should be taken at approximately the same time each day. Dexamethasone should be taken approximately 1 hour after MLN9708. Each dose of dexamethasone should be taken with food or milk.

If a dose of dexamethasone is missed, the dose should be taken as soon as the patient remembers it. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

6.2 Reference/Control Therapy

There is no reference group in this study.

6.3 Definitions of Dose-Limiting Toxicity (DLT)

6.3.1 DLT Definitions

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment must influence decisions regarding dose-escalation, expansion of a dose level, or evaluation of intermediate dose levels. However, DLTs occurring in later cycles may be taken into consideration for dose-escalation decisions, at the discretion of the investigators and sponsors.

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.[58] Toxicity will be evaluated

according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.[58] DLT will be defined as any of the following AEs that are considered by the investigator to be even possibly related to therapy with MLN9708:

- Any Grade 4 thrombocytopenia (platelets < 25, 000/mm^3) lasting at least 7 days.
- Grade 3 thrombocytopenia with clinically significant bleeding, where clinically significant bleeding is defined as a blood loss of ≥ 100 cc or the requirement for a RBC transfusion.
- A platelet count < 10,000/mm^3.
- Any Grade 4 neutropenia (ANC < 500/mm^3) lasting at least 7 days or Grade 3 febrile neutropenia with fever and/or infection where fever is defined as a temperature ≥ 38.5°C.
- Grade 2 peripheral neuropathy with pain or Grade 3 or greater peripheral toxicity.
- Any Grade 3 or higher nonhematologic toxicity (in particular, worsening neuropathy, diarrhea despite maximal supportive therapy, life-threatening ventricular arrhythmia or atrial arrhythmia with hemodynamic instability, fluid retention that does not resolve with 3 or 4 days of intravenous diuretic therapy and bedrest, symptomatic congestive heart failure, and hypotension); with the following exceptions: Grade 3 arthralgia/ myalgia and brief (< 1 week) Grade 3 fatigue.
- Grade 3 or greater nausea and/or emesis despite the use of optimal anti-emetic prophylaxis. Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen than employs 5-HT_3 antagonist given according to standard practice.
- A delay of more than 2 weeks in the initiation of Cycle 2 of treatment because of a lack of adequate recovery of MLN9708-related hematological or nonhematologic toxicities.

- Other MLN9708-related nonhematologic toxicities Grade 2 or greater that, in the opinion of the investigator, requires discontinuation of therapy with MLN9708.

Patients who do not receive all doses of MLN9708 in Cycle 1 for reasons other than DLTs will be replaced within the cohort. Patients who receive all doses of MLN9708, yet for unforeseen circumstances recovery of toxicity is not available and safety in Cycle 1 cannot be fully evaluated may be replaced within the cohort.

6.4 Dose-escalation Rules

The dose intervals will follow the 3+3 traditional escalation rules, starting with the treatment of 3 patients at a planned dose level:

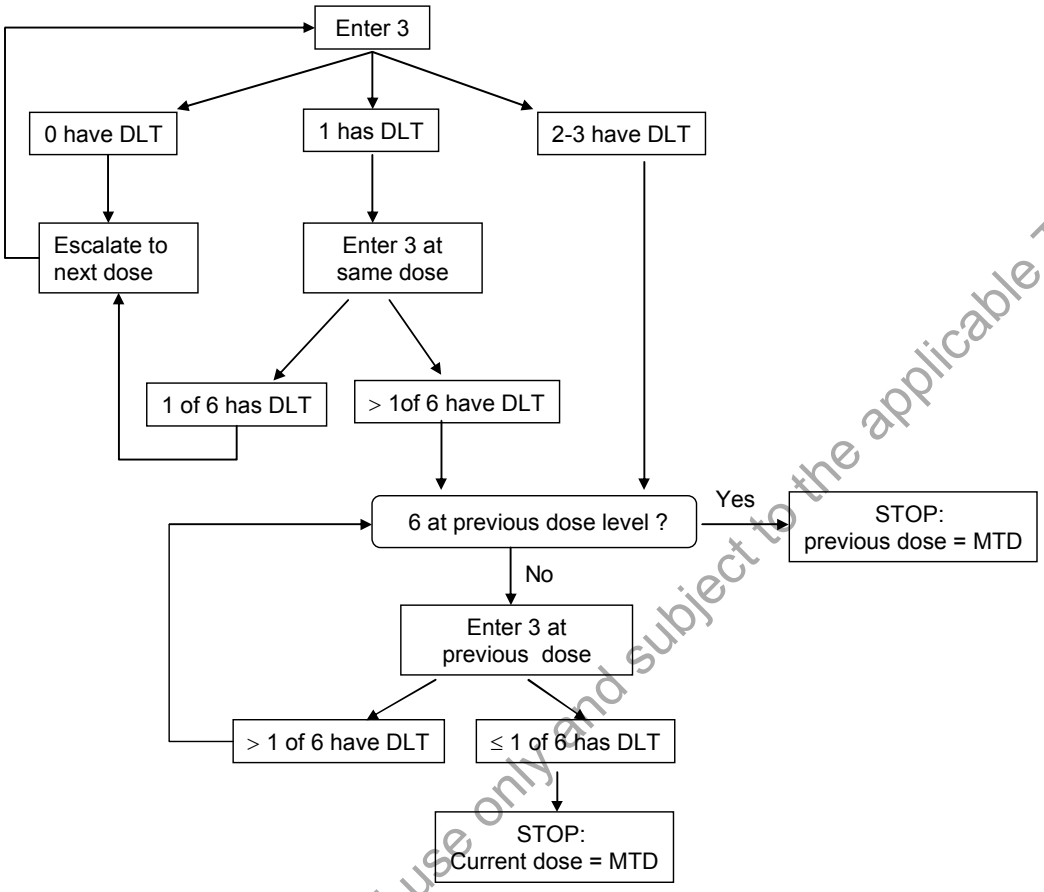
1. If 0 of 3 patients experiences DLT, dose-escalation will proceed to the next higher dose level at which 3 patients will be enrolled.

2. If 1 of 3 patients experiences DLT, 3 more patients will be enrolled at that same dose level.

3. Escalation will continue if 1 of 6 patients experiences DLT.

4. If 2 or more patients in any dose level experience DLT, dosing will stop, and the previous dose level may be considered the MTD or an alternative dose between this dose level and the previous dose level might be further explored.

Figure 6-1 Dose-escalation Algorithm



Planned Dose Levels of MLN9708

The estimated safe starting dose of MLN9708 was selected from the dose-escalation portion of the C16004 study, a phase 1 study of weekly dosing in patients with relapsed and refractory multiple myeloma. The starting dose for Study C16007 was to be either at least 1 dose level below the MTD from Study C16004 if it had been determined and, if not, then a dose level completed without DLTs. The starting dose of 4.0 mg (flat dose) is dose level 2 as seen in Table 6-1. This dose represents a dose completed without reported DLTs in Study C16004 since the MTD has not been determined in that study.

A population PK analysis was performed for MLN9708 to assess the feasibility of switching from BSA-based dosing to flat dosing. A population PK model was built using nonlinear mixed effects modeling in NONMEM VII software compiled with the Intel Fortran 9.2 compiler. Data from both the twice weekly and once weekly IV dosing regimens were used in the analysis (N = 42). Population PK analysis showed that MLN9708 PK can be well described by a 3-compartment model with linear elimination. Race, sex, BSA, and/or body

weight do not appear to significantly affect clearance (CL) and volume of distribution (V_1) in the central compartment. Clearance and volume of distribution in the central compartment are the PK parameters that will affect AUC and C_{max}, respectively. CL and V_1 are primary parameters that are independent of the route of administration of drug. Therefore, BSA is not expected to affect C_{max} or AUC after oral dosing, and thus flat dosing is appropriate for both oral and IV routes of administration.

The planned dose levels of MLN9708 are shown in Table 6-1. The starting dose level in this study is Dose Level 2 (4.0 mg).

Table 6-1 Planned Dose Levels

Dose Level	Dose MLN9708 (mg)
1	3.0
2	4.0
3	5.5
4	7.0
5+	prior dose × 1.33

Note: More conservative dose-escalation, evaluation of alternative doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics of MLN9708. If emerging data from other MLN9708 phase 1 studies support it, consideration could be given to an alternative dosing schedule, eg, twice weekly, if such a measure is needed to better characterize safety and activity.

Note: The dose levels of MLN9708 shown in this table represent possible estimated doses planned in this study based on those already safely administered to patients treated to date in the C16004 study in which BSA dosing was used.

Based on experience with other drugs for this disease, it is considered unlikely that patients with systemic AL amyloidosis will tolerate doses higher than those tolerated in other diseases, such as multiple myeloma. Therefore, the MTD in patients with systemic AL amyloidosis may be the maximum dose as recommended from the phase 1 single-agent study of weekly MLN9708 in relapsed or refractory multiple myeloma (C16004).

More conservative dose-escalation, evaluation of alternative dosing, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics of MLN9708. If emerging data from other MLN9708 phase 1 studies support it, consideration could be given to an alternative dosing schedule, eg, twice weekly, if such a measure is needed to better characterize safety and activity.

Recommendation of Phase 2 Dose

The RP2D estimation will be established following evaluation of the available data which will include, but is not limited to, toxicity characterization (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, and treatment discontinuation) with efficacy (hematologic and organ responses) also taken into consideration. The RP2D will require first cycle DLTs in not more than 0 in 3 or 1 in 6 DLT-evaluable patients enrolled in a single cohort. For the purpose of the RP2D estimation, Cycle 1 data from 6 evaluable patients will be used in addition to the available clinical data supporting tolerance over multiple treatment cycles. AEs that meet DLT criteria in Cycle 2 and beyond will not necessarily influence dose-escalation, but will be considered when determining the RP2D. Toxicities leading to dose modification in Cycle 2 and beyond will not necessarily influence dose-escalation, but will be considered when determining the RP2D.

Once the MTD/RP2D has been established, 2 expansion cohorts of patients with relapsed or refractory amyloidosis, including approximately 10 proteasome inhibitor-naïve patients and approximately 16 proteasome inhibitor-exposed patients, will be treated at the MTD/RP2D to more fully characterize the safety, tolerability, and efficacy of MLN9708, and the PK and pharmacodynamics of MLN9708 in this patient population. As many as 30 patients will be enrolled in the dose-escalation portion of the study, and as many as 20 additional patients (26 in total, including 6 patients from the dose-escalation portion) will be enrolled in the expansion cohorts.

6.5 Dose-Modification Guidelines

6.5.1 Dose-Modification Guidelines

During the study, the focus of the evaluations is on the assessment of toxicity to document the occurrence of DLT. Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment must influence decisions regarding dose-escalation, expansion of a dose level, or evaluation of intermediate dose levels. However, DLTs occurring in later cycles may be taken into consideration for dose-escalation decisions, at the discretion of the investigators and sponsors. Unless a DLT is documented to have occurred, no dose modification is allowed during Cycle 1. Dose-limiting toxicities (DLTs) are defined in Section 6.3.1. In the event that a patient experiences DLT during Cycle 1, treatment should be held and the event will be counted toward the assessment of MTD for the given cohort. Patients experiencing DLTs in Cycle 1 may be restarted following recovery from toxicity at the discretion of the investigator according to the guidelines provided in Section

6.5.2 and Section 6.6. If a decision is made to restart MLN9708 therapy following a DLT, the MLN9708 dose must be reduced 1 dose level.

The patient will be evaluated weekly for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI CTCAE, version 4.03.[58] Prior to beginning the next cycle of treatment, refer to the guidelines in Sections 6.5.2 and 6.6. Further clarification can be obtained in consultation with the Millennium clinician (or designee). If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines.

6.5.2 Criteria for Toxicity Recovery Before Beginning the Next Cycle of Treatment

If a patient fails to meet the criteria outlined in the following sections for beginning the next cycle of treatment, initiation of the next cycle should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. If the start of the next cycle needs to be delayed for more than 2 weeks due to incomplete recovery from treatment-related toxicity, refer to the recommended dose modification guidelines provided in Section 6.6. The maximum delay before treatment should be discontinued will be 3 weeks (except in the case of investigator determined clinical benefit and discussion with the Millennium clinician).

NOTE: A delay of more than 2 weeks because of lack of adequate recovery of MLN9708-related hematologic or nonhematologic toxicities occurring during Cycle 1 meets the criteria for a DLT in the given cohort (refer to Section 6.3). If the patient is to receive additional treatment despite a DLT, the dose of MLN9708 will be reduced by at least 1 dose level (or by 33% if the patient is receiving the first dose level) upon resolution of toxicity (refer to Section 6.6).

6.5.2.1 Criteria for Hematologic and Nonhematologic Recovery

- Absolute neutrophil count (ANC) must be $\geq 1 \times 10^9$/L
- Platelet count must be $\geq 75 \times 10^9$/L
- All other nonhematologic toxicity (except for alopecia) must have resolved to $\leq$ Grade 1 or to the patient's baseline condition

6.6 Criteria for Dose Modification (Delays, Reductions, and Discontinuations)

When possible, toxicities should be attributed to a specific study drug (MLN9708 or dexamethasone [as applicable]) so that dose modifications can be made rationally. If multiple toxicities are noted, the dose adjustments and/or delays should be made once per cycle according to the most severe toxicity guidelines.

6.6.1 MLN9708 Dose Adjustments for Hematologic Toxicity

Dosage adjustments for hematologic toxicity are outlined in Table 6-2.

Table 6-2 MLN9708 Dose Adjustments for Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
If platelet count ≤ 30×10^9/L or ANC ≤ 0.75×10^9/L on a MLN9708 dosing day (other than Day 1)	MLN9708 dose should be withheld. Complete blood count (CBC) with differential should be repeated at least every other day until the ANC and/or platelet counts have exceeded the prespecified values (see Section 6.5.2.1) on at least 2 occasions. In the event CBC cannot be repeated at least every other day, dose modifications should be made in consultation with sponsor. Upon recovery, MLN9708 may be reinitiated with 1 dose level reduction or by 33% if the patient is receiving the first dose level.
Dose Modifications for Subsequent Treatment Cycles	
Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 6.5.2: - ANC < 1.0×10^9/L, platelet count < 75×10^9/L, or other nonhematologic toxicities > Grade 1 or not to the patient's baseline condition	- Hold MLN9708 until resolution as per criteria Section 6.5.2. - Reduce MLN9708 1 dose level or 33% if the patient is receiving the first dose level. - The maximum delay before treatment should be discontinued (except in the case of investigator determined clinical benefit and discussion with the Millennium clinician) will be 3 weeks.
Dose Modifications for Subsequent Treatment Cycles	
All hematologic toxicities	For hematologic toxicity that occurs during a cycle but recover in time for the start of the next cycle, a dose level reduction will be made either based on within-cycle or for

Table 6-2 MLN9708 Dose Adjustments for Hematologic Toxicities

Criteria	Action
	subsequent cycle criteria, but not for both from the same cycle.

6.6.2 MLN9708 Dose Adjustments for Nonhematologic Toxicity

Dosage adjustments for nonhematologic toxicity are outlined in Table 6-3.

Table 6-3 MLN9708 Dose Adjustments for Nonhematologic Toxicities

Criteria	Action
Peripheral Neuropathy:	
Newly developed Grade 1 peripheral neuropathy with pain, Grade 2 peripheral neuropathy,	Reduce dose of MLN9708 to the previous dose level or by 33% if the patient is receiving the first dose level.
Grade 2 neuropathy with pain or Grade 3 peripheral neuropathy	Hold MLN9708 until toxicity resolves or returns to baseline. When toxicity resolves, re-initiate MLN9708 at the previous dose level or by 33% if the patient is receiving the first dose level.
Grade 4 peripheral neuropathy	Discontinue MLN9708. Peripheral neuropathy should be monitored until toxicity resolves or returns to baseline. Upon toxicity recovery, if the patient has received clinical benefit from therapy with MLN9708, the investigator and Millennium clinician may consider restarting therapy.
All Other Grade ≥ 3 Nonhematological Toxicities, except: - ≥ Grade 3 nausea and/or vomiting in the absence of optimal anti-emetic prophylaxis (Section 6.10) - ≥ Grade 3 diarrhea that occurs in the absence of optimal supportive therapy (Section 6.10) - Grade 3 fatigue	- Hold MLN9708 until resolution to Grade < 1 or baseline. - Reduce MLN9708 1 dose level or 33% if the patient is receiving the first dose level. - Note, a dose level reduction will be made either based on within-cycle or for a subsequent cycle criteria, but not for both from the same cycle.
Grade 4 Nonhematologic Toxicities	Consider permanently discontinuing MLN9708. Exception, in the case where the investigator determines the patient is obtaining a clinical

Table 6-3 MLN9708 Dose Adjustments for Nonhematologic Toxicities

Criteria	Action
	benefit and has discussed this with the Millennium clinician.
Criteria for Retreatment and Cycle Delays	
Both hematologic & nonhematologic recovery required	Delay therapy × 1 week. Re-evaluate patient; if still not resolved, delay therapy × 1 additional week.
If not resolved	If initiation of subsequent therapy needs to be delayed for more than 2 weeks because of incomplete recovery from treatment related toxicity, the dose of MLN9708 will be reduced by at least 1 dose level when treatment resumes. The maximum delay before treatment should be discontinued (except in the case of investigator-determined clinical benefit and discussion with the Millennium clinician) will be 3 weeks.

6.6.3 Dexamethasone–Related Treatment Modification

Dosage adjustments for dexamethasone are outlined in Table 6-4**.** Dexamethasone dose treatment modifications are outlined in Table 6-5.

Table 6-4 Dose Reduction Steps for Dexamethasone

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
40 mg QD	20 mg QD	8 mg QD	Discontinue dexamethasone

Table 6-5 Dexamethasone–Related Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Due to Adverse Events

Adverse Event (Severity)		Action on Study Drug
Gastrointestinal	Dyspepsia, gastric, or duodenal ulcer, gastritis Grades 1-2 (requiring medical management)	Treat with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, decrease dexamethasone by 1 dose level.
	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease 1 dose level of current

Table 6-5 Dexamethasone–Related Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Due to Adverse Events

Adverse Event (Severity)		Action on Study Drug
		dose along with concurrent therapy with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema > Grade 2 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed and decrease dexamethasone by 1 dose level. If edema persists despite these measures, decrease dose another level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurological	Confusion or mood alteration > Grade 2	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness > Grade 2 (interfering with function ± interfering with activities of daily living)	Decrease dexamethasone dose by 1 dose level. If weakness persists despite these measures, decrease dose by 1 dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite these measures, decrease dose by 1 dose level until levels are satisfactory.

Source: Package insert for DEXAMETHASONE Tablets USP, DEXAMETHASONE Oral Solution September 2007, Roxane Laboratories, Inc, a division of Boehringer Ingelheim.[59]

6.7 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study.

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study. The rationale for this is that in the event of a drug-drug interaction with an inhibitor, MLN9708 exposure would be increased leading to a high probability of an AE.

- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use. The rationale for this (unlike with inhibitors) is that in the event of a drug-drug interaction with an inducer, MLN9708 exposure would be decreased, leading to a reduced chance of toxicity and potentially a reduced chance of efficacy.

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
- ACE inhibitors (ACE inhibitors should be used with caution and requires consultation with the Millennium clinician. Patients with AL amyloidosis usually poorly tolerate ACE inhibitors, not due to possible interaction with MLN9708, but because of symptomatic hypotension due to an underlying involvement of the autonomic nervous system. Therefore, ACE inhibitors should be excluded in patients with eGFR < 60mg/min/1.72 and in those whom orthostatic systolic blood pressure is < 100 mmHg.)
- Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba
- Warfarin (aspirin is allowed)

The following procedures are prohibited during the study:

- Any antineoplastic treatment with activity against AL amyloidosis, other than study drugs

- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)

- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing

6.8 Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care shall be available to patients as necessary.

The following are examples of those permitted during the study:

Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) will not be allowed in Cycle 1, but may be considered in Cycle 2 and beyond although caution must be exercised.

Patients should be transfused with red cells and platelets as clinically indicated.

Antiviral therapy such as acyclovir may be considered.

Concomitant treatment with bisphosphonates will be permitted.

Patients who experience worsening neuropathy from baseline may be observed for recovery, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator. Dose reduction is suggested, when and if the patient resumes MLN9708 therapy.

Standard amyloid supportive guidelines that should be considered include:

Patients who experience fluid retention or congestive heart failure (CHF) may be treated with intravenous diuretics.

Patients who experience life-threatening ventricular arrhythmias or atrial arrhythmias with hemodynamic instability should be treated according to standard clinical practice guidelines

Compression garments and midodrine for patients with symptomatic orthostasis

Note: Such adverse events may still qualify as a DLT depending on the severity and timing of their occurrence (see Section 6.3.1).

6.9 Precautions and Restrictions

It is not known what effects MLN9708 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 30 days after the last dose of study drug, or agree to completely abstain from heterosexual intercourse

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
- Agree to completely abstain from heterosexual intercourse

Additionally, volume depletion should be corrected before initiation of study drug.

NSAIDs should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

6.10 Management of Clinical Events

Prophylaxis Against Risk of Infection

If lymphopenia is noted, patients may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster and herpes simplex

viruses. Antiviral therapy such as acyclovir or valacyclovir may be initiated at the onset of administration of MLN9708. Other antivirals are also acceptable.

Erythematous Rash With or Without Pruritus

As with VELCADE, rash with or without pruritus has been reported with MLN9708, primarily at the higher doses tested. The rash has been transient and has resolved either spontaneously or with standard symptomatic measures such as oral or topical antihistamines. Prophylactic measures should also be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone < 10 mg per day or equivalent [See Section 6.13]) is permitted. In the case of rash, punch biopsies for histopathological analysis are encouraged at the discretion of the investigator. In the event a skin biopsy specimen is collected, excess tissue should be sent to the sponsor (or designee). This tissue may be utilized for conducting additional histopathological analysis and/or pharmacodynamic assessments.

Nausea and/or Vomiting

Standard anti-emetics including 5 HT3 antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered. Dexamethasone should not be administered as an anti emetic. Volume depletion should be corrected before initiation of study drug.

Diarrhea

Prophylactic antidiarrheals will not be used in Cycle 1 of this protocol unless the patient has AL amyloidosis involving the GI tract (see Section 5.2). However, the administration of antidiarrheals once infectious causes are excluded may be considered. Fluid intake should be maintained to avoid dehydration. Volume depletion should be corrected before initiation of study drug.

Thrombocytopenia

Thrombocytopenia has been reported to date primarily at the higher doses tested. Blood counts should be monitored regularly as outlined in each protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Administration of MLN9708 should be modified as noted as per dose modification

recommendations in each specific protocol when thrombocytopenia occurs. Therapy with MLN9708 can be reinitiated at a reduced level upon recovery of platelet counts.

Volume Depletion

Dehydration should be avoided. Two cases of acute renal failure have been reported in patients treated at or above the MTD for IV MLN9708 (see Section 1.3). Volume depletion should be corrected before initiation of study drug. Until further information is available, intake of nonsteroidal anti-inflammatory drugs immediately prior to the administration of MLN9708 should be discouraged and requires consultation with the Millennium clinician.

6.11 Blinding and Unblinding

This is an open-label study; no blinding methods will be employed.

6.12 Description of Investigational and Noninvestigational Medicinal Agents

6.12.1 MLN9708: Investigational Medicinal Agent

The drug product is MLN9708 capsules. The drug product is provided in strengths of 0.2-, 0.5-, and 2.0-mg capsules as the active boronic acid.

The 3 different dose strengths are differentiated by both capsule size and color as described in Table 6-6.

Table 6-6 MLN9708 Capsules

Dose Strength	Capsule Size	Capsule Color
0.2 mg	Size 4	White opaque
0.5 mg	Size 3	Dark green
2.0 mg	Size 2	Swedish orange

For additional details, please see the MLN9708 IB and pharmacy manual.

6.12.2 Dexamethasone: Noninvestigational Medicinal Agent

Dexamethasone is a standard agent. It is a commercially-available oral drug supplied as tablets.

6.13 Preparation, Reconstitution, and Dispensation

MLN9708

MLN9708 is an anticancer drug and as with other potentially toxic compounds caution should be exercised when handling MLN9708 capsules.

Dexamethasone

Dexamethasone is a standard agent and will be procured from commercial sources. Additional details are provided in the package insert or SmPC as appropriate.

6.14 Packaging and Labeling

The study drug MLN9708 capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations. The formulation consists of 0.2-, 0.5-, and 2.0-mg capsules for oral administration.

The capsules are individually packaged in blisters using cold form foil-foil with child resistant paper backing. The capsules are in 1 × 4 blister strips that are individually perforated. The strips (1 × 4) are placed in cartons containing 6 strips (24 total capsules) of the same strength.

6.15 Storage, Handling, and Accountability

Upon receipt at the investigative site, MLN9708 should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). All excursions should be brought to the sponsor's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, MLN9708 capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above

until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Approval for any patient for take-home medication must be discussed with Millennium in order to ensure the greatest conformity with repackaging, labeling, and patient compliance. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F-46°F, 2°C-8°C) for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because MLN9708 is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact. The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of MLN9708, including that MLN9708 is to be taken as intact capsules.

Please refer to the pharmacy manual for additional instructions.

Dexamethasone

Dexamethasone tablets should be stored in accordance with the package insert or SmPC. requirements.

Dexamethasone will be made available in an amount sufficient for each treatment cycle.

6.16 Other Protocol-Specified Materials

No other drugs or ancillary material are supplied for use in this study.

7. STUDY CONDUCT

7.1 Study Personnel and Organizations

The contact information for the central laboratory and any additional clinical laboratories may be found in the Study Manual.

Emergency contact information for the study's medical monitors is provided below with additional information also in the Study Manual:

EU: +371 6709 5803
US and Canada: +1 888-723-9952

For use in Italy only

Emergency contact numbers for the study doctors will be provided to patients in the Subject Information Sheet Informed Consent Form (SISICF). Additionally emergency contact numbers are provided in the study manual.

7.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

During the dose escalation phase of the study patients will be assigned to a dose level based on the dose-escalation methodology as described in Section 6.4. All patients in the expansion portion will be assigned the same initial dose level.

7.4 Enrollment

Enrollment in this study is defined as the time the patient receives the first dose of study drug.

Procedures for completion of the enrollment information are described in the Study Manual.

7.5 Study Procedures

Patients will be evaluated at scheduled visits over 4 study periods: Screening, Treatment, End of Treatment (EOT), and Follow-Up (progression-free and overall survival). Refer to the Schedule of Events for the timing of all procedures.

Additional details are provided as necessary in the sections that follow.

7.5.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.5.2 Patient Demographics

The age, race, ethnicity, and sex of the patient are to be recorded during screening.

7.5.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. A complete medical history is to be obtained at screening, including AL amyloidosis diagnosis, staging (cardiac biomarkers and NYHA classification), AL amyloidosis organ involvement, treatment history, neurologic medical history, and cardiac medical history. The history should include a review of all current medications and the patient's current smoking status.

7.5.4 Physical Examination

A complete physical examination is to be conducted at the Screening visit and at the time points specified in the Schedule of Events. A neurologic examination is to be conducted to assess both amyloid-related clinical findings and treatment emergent adverse events; Symptom-directed assessments will be conducted per standard clinical practice to include but not limited to visits for response assessment.

7.5.5 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG scale (see Section 15.3) at the time points specified in the Schedule of Events.

7.5.6 Vital Signs, Body Weight, and Height

Measurement of vital signs will include temperature, blood pressure, and heart rate. Consideration should be given to determining orthostatic hypotension in patients with amyloid nerve involvement.

Body weight will be determined at the Screening visit and the time points specified in the Schedule of Events. Height will be measured at the Screening visit only.

7.5.7 Pregnancy Test

A serum pregnancy test will be performed for all women of childbearing potential at the Screening visit; Cycle 1, Day 1 (predose). The Cycle 1, Day 1 pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the first dose of MLN9708 is administered.

Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations.

7.5.8 Electrocardiogram

A 12-lead ECG will be conducted at screening and at the times outlined in the Schedule of Events. It may be repeated as clinically indicated during the study at the discretion of the investigator. ECG data to be obtain include intervals RR, PR, QRS, QT, and QTc and waveforms.

7.5.9 Holter Cardiac Monitor

Continuous cardiac monitoring will be conducted for 24 hours during screening using a Holter Monitor. It may be repeated as clinically indicated during the study at the discretion of the investigator.

7.5.10 Clinical Laboratory Evaluations

Handling of clinical laboratory samples will be outlined in the Study Manual. Decisions regarding eligibility for this study may be made using local laboratory determinations. For dosing decisions, local hematology and chemistry laboratory results may be used. Hematology and chemistry panels may be collected up to 72 hours prior to dosing. Criteria for retreatment are provided in Section 6.6.

Clinical Chemistry and Hematology

Blood samples for analysis of the following clinical chemistry and hematological parameters will be obtained as specified in the Schedule of Events. After 24 cycles on treatment, hematology and chemistry laboratory evaluations may be done to monitor the patient according to standard clinical practice per the treating physician.

Hematology

- Hemoglobin
- Hematocrit
- Platelet count
- WBC count with differential

Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Total bilirubin
- Uric acid
- Lactate dehydrogenase
- Alkaline phosphatase
- AST
- ALT
- Albumin
- Glucose
- Sodium
- Potassium
- Chloride
- CO_2
- Magnesium
- Calcium
- Phosphate

Urinalysis

- Appearance and color
- pH
- Specific gravity
- Protein
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Glucose
- Leukocytes
- Microscopic assessment

24-Hour Urine Collection

- Total protein
- Creatinine

Coagulation Studies

- Prothrombin time and international normalized ratio
- Activated partial thromboplastin time

Hormones

- Thyrotropin (TSH)
- Cortisol

Other

- Cardiac Markers: BNP, NT-ProBNP, and troponin T or I
- β2-microglobulin

7.5.11 Quality of Life Assessment (European Organization for Research and Treatment of Cancer)

For Patients Enrolled in the Expansion Cohort Only

The QOL Assessment (EORTC-QLQ-C30; see Section 15.6) will be completed by the patient at screening and at the time points specified in the Schedule of Events.

7.5.12 Disease Assessments

7.5.12.1 Hematologic Disease Assessments

The primary determinant of response for the purpose of continuing treatment is the hematologic response. Response will be determined according to standardized criteria using a central laboratory. A bone marrow aspirate and biopsy are to be obtained at the Screening visit and may be repeated at the discretion of the investigator as clinically indicated and at the EOT. Immunohistochemistry of dominant clonal plasma cells is recommended. The response assessment is to be done during the rest cycle period (Days 22 through 28)

Quantitative Immunoglobulins, Serum M-protein, Urine M-protein, and Serum Free Light Chains

Serum specimens will be analyzed for quantitative immunoglobulins at screening, and if abnormal at screening, this test is to be repeated during Days 22 through 28 of each treatment cycle, and at the EOT visit. If the patient comes off treatment, but has not yet progressed it should be conducted every 6 weeks until disease progression.

Analysis for serum and urine M-protein and immunofixation is to be performed at screening, during Days 22 through 28 of each treatment cycle, and at the EOT visit. If the patient comes off treatment, but has not yet progressed it should be conducted every 6 weeks until disease progression.

Serum free light chain assay and ratio is to be performed at screening, during Days 22 through 28 of each treatment cycle, and at the EOT visit. If the patient comes off treatment, but has not yet progressed it should be conducted every 6 weeks until disease progression. The definition of hematologic response to treatment is based on the difference between the concentration of amyloid forming (involved) and uninvolved free light chain (dFLC). To be measurable dFLC must be at least 50 mg/L. Patients with dFLC < 50 mg/L are eligible for clinical studies but are evaluable only for complete remission.[55, 56]

7.5.12.2 Amyloid-Related Organ Assessments

Amyloid-related organ assessments (see Section 15.7) are to be performed for all patients at screening; after Cycles 3, 6, 9, and 12; every 6 months thereafter until disease progression; and at the End-of-Study visit (as outlined in the Schedule of Events).

The following procedures/ tests should be included at a minimum to assess amyloid-related organ involvement. If clinically indicated, additional assessments may be performed at the discretion of the investigator.[23, 54, 55, 56]

Heart: NT-proBNP, BNP, troponin, echocardiography, physical examination

Kidney: 24-hour urine proteinuria, serum creatinine, eGFR, serum albumin

Liver: alkaline phosphatase, ALT, ultrasound/CT scan/ MRI (as indicated)

Peripheral nervous system: patient reported symptoms, physical examination, electromyography (EMG) (if indicated)

Autonomic nervous system: patient reported symptoms, determination of postural hypotension

Soft tissue: physical examination, imaging as indicated

These assessments include relevant AEs and patient-reported symptoms, physical findings, and special laboratory tests for individual organ sites. In addition, radiographic, CT, MRI,

and ultrasound techniques may be performed as indicated to assess organ involvement. In some cases, tissue sampling may be necessary. Detailed cardiac evaluations are planned. At each staging evaluation, the organ response/improvement will be assessed relative to baseline.

Cardiac Assessments

Cardiac assessments are to be performed for all patients as outlined in the Schedule of Events.

The assessments include, but are not limited to:

- Relevant AEs and clinical findings, such as dyspnea, fluid retention, fatigue
- Cardiac markers (NT-proBNP and troponin T or I)
- Blood pressure
- NYHA classification determination (see Section 15.4)
- Echocardiogram at baseline; Cycles 3, 6, 9, and 12; and every 6 months thereafter until disease progression

The following data may be collected: 2D-guided M-Mode (wall thickness and chamber diameters), short-axis, long-axis, apical 4-chamber and 2-chamber video clips (5 beats each), transmitral, transaortic, transtriscupidal, and pulmonary vein Doppler studies, mitral and tricuspidal annulus longitudinal excursion, tissue Doppler imaging for systolic and diastolic wall velocities. Strain and strain rate analyses -may also be analyzed off-line from the short-axis and 4-chamber video clips at the discretion of the investigator.

> Note: The average of the estimates of the interventricular septal and posterior wall thickness yields the mean ventricular wall thickness.

Note: If CT or MRI cardiac assessments are clinically indicated, then a record of the findings will be made.

Renal Assessment:

- 24-hour urine collection (total protein, M-protein quantification, and immunofixation)
- eGFR assessment

- Serum creatinine
- Serum albumin

Renal assessments are to be performed in all patients as outlined in the Schedule of Events.

Hepatic Assessment

- Alkaline phosphatase
- Clinical examination, or
- Abdominal ultrasound, or
- CT or MRI scans at the discretion of the investigator as clinically indicated.

Hepatic assessments are to be performed in all patients as outlined in the Schedule of Events. The same evaluation (physical examination or radiography [and the same imaging modality]) must be used consistently in individual patients throughout the study for all follow-up assessments.

Neurologic Assessments

Assessments are to be performed in all patients as outlined in the Schedule of Events.

- Patient-reported gastrointestinal and neurologic symptoms
- Clinical examination
- Neurologic examination, including sensory and/or motor findings
- Nerve conduction studies, if indicated (including electromyography, if necessary)
- Detection and measures of postural hypotension

Soft Tissue or Lymph Node

Assessments are to be performed in all patients as outlined in the Schedule of Events.

- CT or MRI scans at the discretion of the investigator as clinically indicated. The same imaging modality used at screening (CT/MRI) should be used for all follow-up assessments
- Recording of any abnormalities on physical examination

- Patient reported symptoms

The investigator will evaluate each patient for response to therapy according to the response criteria presented in Sections 15.8 and 15.9. At each staging evaluation, the organ response will be assessed relative to baseline.

7.5.13 Pharmacokinetic and Pharmacodynamic Measurements

The timing of the PK and pharmacodynamic blood specimens may be changed if emerging data indicate that an alteration in the sampling scheme is needed to better characterize the PK or pharmacodynamics of MLN9708. The number of specimens may also change, but the number will not increase.

Plasma concentrations of the complete hydrolysis product of MLN9708 (ie, MLN2238) will be measured using a GLP-validated liquid chromatography/tandem mass spectrometry assay. Whole blood concentrations of MLN2238 will be measured using a fit-for-purpose liquid chromatography/tandem mass spectrometry assay.

Details regarding the preparation, handling, and shipping of the PK and pharmacodynamic samples are provided in the Study Manual.

The sampling scheme is outlined in the Pharmacokinetic & Pharmacodynamic Sampling (Cycle 1). One blood sample (3 mL) for the determination of plasma concentrations of MLN2238, 1 blood sample (3 mL) for the determination of whole blood concentrations of MLN2238, and 1 blood sample (1 mL) for the measurement of whole blood 20S proteasome activity will be collected at each time point. Blood samples are to be collected during Cycle 1 at the following time points before and after the administration of MLN9708 on Day 1 (MTD cohort patients only) and Day 15 (all patients enrolled in the study): predose (within 1 hour before dosing), and postdose: 30 (± 5) minutes, 1 (± 0.25) hour, 2 (± 0.25) hours, 4 (± 0.75) hours, 6 (± 0.75) hours, 24 (± 1.0) hours (Days 2 and 16), and 168 (± 4.0) hours (Days 8 and 22). If feasible, a blood sample for plasma concentration should also be obtained at the time of any drug-related SAE.

7.5.14 Germline DNA Measurements

CCI

Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

7.5.14.1 Tumor Biomarkers Assessment

CCI

[redacted]

7.5.15 Concomitant Medications and Procedures

Concomitant medications and therapy will be recorded as specified in the Schedule of Events. See Section 6.7 for a list of prohibited concomitant medications and therapies and Section 6.8 for a list of allowed concomitant medications and therapies.

7.5.16 Adverse Events

Monitoring of AEs, both nonserious and serious, will be conducted throughout the study as specified in the Schedule of Events. See Section 10.1 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.5.17 Follow-Up Assessments (PFS and OS)

Patients who do not develop PD will continue to have PFS follow-up visits. The hematologic PFS follow-up should occur every 6 weeks from the EOT until the occurrence of progression or the start of subsequent antineoplastic therapy. A bone marrow aspirate and biopsy may be repeated at the discretion of the investigator as clinically indicated, but is not required during this follow-up period. The amyloid-organ PFS follow-up assessments should occur every 6 months from the EOT until the occurrence of progression (including hematologic progression) or the start of subsequent antineoplastic therapy. Refer to the Schedule of Events and Section 7.5.12 for appropriate assessments.

After the occurrence of PD or the initiation of subsequent antineoplastic therapy, patients will continue to have OS follow-up visits. The OS follow-up visits should be conducted every 12 weeks after documented PD or until the initiation of subsequent antineoplastic therapy. Data may be collected by methods that include, but are not limited to, telephone, e-mail, mail, and social security indexes. The duration of follow-up for OS will be 60 months after the last patient starts treatment.

7.6 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

7.7 Completion of Treatment

Patients will be considered to have completed study treatment if they meet any of the following criteria:

- Have received at least 6 cycles of treatment
- PD after at least 28 days of Cycle 1

7.8 Completion of Study

Patients will be considered to have completed the study if they complete treatment according to the criteria outlined in Section 7.7 and complete 6 months of follow up (after the last dose of MLN9708).

7.9 Discontinuation of Treatment With Study Drug, and Patient Replacement

For patients who did not complete treatment by meeting 1 or more of the criteria outlined above, treatment may be discontinued permanently if any of the following criteria are met:

- AE
- Protocol violation
- Study terminated by sponsor
- Withdrawal by patient
- Lost to follow-up
- PD
- Initiation of subsequent therapies
- Progression of amyloid markers (hematologic), see Section 15.9.
- Clinically important decrease in ECOG performance status with organ function deterioration

- Other

At the time of study drug discontinuation, all study procedures outlined for the EOT visit will be completed. The primary reason for study drug discontinuation will be recorded on the electronic case report form (eCRF). Patients who do not meet the DLT-evaluable criteria in the dose-escalation part of the study may be replaced. See Section 8.1.3 for definitions of patient populations of the study.

Patients who are withdrawn from treatment during Cycle 1 for reasons other than DLT may be replaced.

7.10 Withdrawal of Patients From Study

A patient may also be withdrawn from the study for any of the following reasons:

- Study terminated by sponsor
- Initiation of subsequent therapies
- Withdrawal by patient
- Lost to follow-up
- Death
- Other

The consequence of study withdrawal is that no new information will be collected from that patient and added to the existing data or any database. However, every effort will be made to follow all patients for safety.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

8.1.1 Determination of Sample Size

A 3 + 3 dose-escalation scheme will be conducted, with 3 to 6 DLT-evaluable patients evaluated at each dose level. It is expected that as many as 30 patients will be enrolled in the dose-escalation part of this study.

Once the MTD/R2PD has been established, the following 2 expansion cohorts will be treated at the MTD or RP2D.

1. Proteasome inhibitor-naive expansion cohort including approximately 8 organ response-evaluable patients. There will be approximately 83% probability of observing at least 2 patients with organ responses among 8 patients based on the binomial probability calculation if the overall organ response rate is 35% for this population. Approximately 10 patients will be enrolled to obtain 8 response-evaluable patients.

2. Proteasome inhibitor-exposed expansion cohort including approximately 14 organ response-evaluable patients. There will be approximately 80% probability of observing at least 2 patients with organ responses among 14 patients based on the binomial probability calculation if the overall organ response rate is 20% for this population. Approximately 16 patients will be enrolled to obtain 14 organ response-evalauble patients.

Because approximately 6 patients in the dose-escalation part of the study will be included in the expansion cohorts, approximately 20 patients will be enrolled in the expansion part of this study.

Overall, as many as 50 patients will be enrolled in this study.

8.1.2 Randomization and Stratification

No randomization or stratification will be performed in this study. All patients from all sites will be pooled for analysis.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

Safety Population: Patients who receive at least 1 dose of MLN9708. The safety population will be used for safety analyses.

DLT-evaluable Population: Patients who receive all Cycle 1 doses of MLN9708 or experience a DLT in Cycle 1. The DLT-evaluable population will be used to determine the MTD.

Organ Response-Evaluable Population: The organ response-evaluable population is defined

as patients who receive at least 1 cycle of MLN9708, have amyloid involvement of at least kidney or heart at baseline, and at least 1 post-baseline organ response assessment.

Hematologic Response-Evaluable Population: The hematologic response-evaluable population is defined as patients who receive at least 1 cycle of MLN9708, have measurable disease at baseline, and at least 1 post-baseline hematologic response assessment.

Plasma PK Analysis Population: Patients who:

a. Receive full doses of MLN9708 during Cycle 1 without dose reduction or interruptions through the completion of PK sampling
b. Do not receive any excluded concomitant medications
c. Have sufficient plasma MLN2238 concentration-time data to permit reliable estimation of plasma PK parameters

Pharmacodynamic Analysis Population: Patients who:

a. Receive full doses of MLN9708 during Cycle 1 without dose reduction or interruptions
b. Do not receive any excluded concomitant medications through the completion of pharmacodynamic sampling
c. Have sufficient whole blood 20S proteasome inhibition-time data to permit reliable estimation of pharmacodynamic parameters

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed.

Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by dose levels of MLN9708 and expansion cohorts. Data to be evaluated will include at least age, sex, race, weight, height, etc. Components of disease severity assessment in addition to relevant patient and disease assessments and laboratory parameters will be presented if appropriate.

8.1.6 Efficacy Analysis

Standard response criteria will be used in this study.[53, 54] The patients treated at doses other than the dose in the expansion cohorts may be combined together for analysis and for presentation in the tables and figures.

The efficacy parameters include the organ response rate and organ improvement rate, overall hematologic response rate, time to hematologic and organ response, duration of hematologic and organ response, time to hematologic and organ response, hematologic and organ disease free progression, and 1-year survival rate.

The organ response and improvement rate will be analyzed based on the organ response-evaluable population. Estimates of the organ response rate will be presented with 2-sided 95% exact binomial confidence intervals.

The hematologic response rate will be analyzed based on the hematologic response-evaluable population and presented with 2-sided 95% exact binomial confidence interval.

Time to organ or hematologic response is defined as the time from the date of the first dose of MLN9708 to the date of first documentation of a confirmed organ or hematologic response, respectively.

Duration of organ or hematologic response is defined as the time from the date of first documentation of a confirmed organ or hematologic response to the date of confirmed organ or hematologic disease progression, respectively.

Time to organ or hematologic disease progression is defined as the time from the date of the first dose of MLN9708 to the date of first documented organ or hematologic disease progression.

Organ or hematologic disease progression free survival is defined as the time from the date of the first dose of MLN9708 to the date of confirmed organ or hematologic disease progression or death, respectively.

One-year survival is defined as the patient survival probability at 1 year after the date of first dose of MLN9708.

Time to response, duration of response, time to progression, PFS, and survival may be analyzed using standard survival analysis techniques based on Kaplan-Meier estimates if appropriate.

8.1.6.1 Exploratory Efficacy Endpoints and Analysis

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[redacted]

8.1.7 Pharmacokinetics, Pharmacodynamics, and Exploratory Analyses

Pharmacokinetic Analysis

PK analysis will be based on concentrations of MLN2238, the complete hydrolysis product of MLN9708.

Individual and mean plasma and whole blood concentration data will be plotted over time. Summary tables will be presented for the plasma and whole blood concentration data. Plasma and whole blood PK parameters will be estimated using noncompartmental analysis methods. The PK parameters calculated for individual plasma MLN2238 concentration-time data and whole blood MLN2238 concentration-time data will include, but are not limited to: C_{max}, T_{max}, and AUC_{tau}. PK parameters will be summarized using descriptive statistics.

Pharmacodynamic Analysis

Individual and mean whole blood 20S proteasome inhibition data will be plotted over time. Summary tabulations will be presented for the whole blood 20S proteasome inhibition data. Pharmacodynamic parameters of whole blood 20S proteasome inhibition will be estimated using noncompartmental analysis methods. The pharmacodynamics parameters calculated for individual whole blood 20S proteasome inhibition-time data will include, but are not limited to: maximum inhibition (E_{max}) and time of occurrence of E_{max} (TE_{max}). Pharmacodynamic parameters will be summarized using descriptive statistics.

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[redacted]

Tumor Biomarker Analysis

CCI

[redacted]

8.1.8 Safety Analysis

Summary tabulations will be presented that will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data.

The incidence of DLT may be tabulated for each dose group. In addition, to assess the relationship between toxicities and MLN9708 dose, the preferred term of individual toxicities may be summarized by their frequency and intensity for each dose group. The DLT-evaluable population will be used for the analysis of DLT. DLT will also be listed for each dose group.

Safety will also be evaluated by the incidence of treatment emergent AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the population evaluable for safety. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent events will be tabulated. Treatment emergent is defined as any AE that occurs after administration of the first dose of study drug and up through 30 days after the last dose of study medication, any event that is considered drug related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline or is subsequently considered drug related by the investigator. AEs will be

tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class, high-level terms, and preferred terms and will include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- Treatment-emergent AEs resulting in study drug reduction
- Treatment-emergent AEs resulting in study drug discontinuation
- SAEs

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients) will be tabulated by high level term and preferred term.

Descriptive statistics for the actual values and/or change from baseline of clinical laboratory parameters will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values and changes from baseline of vital signs, weight, and ECOG scores will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE Grade from baseline to the worst post baseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst post baseline values, may be used to understand the MLN9708 safety profile.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of MLN9708.

8.1.9 Interim Analysis

No formal interim analysis will be conducted in this study.

9. STUDY COMMITTEES

9.1 Steering Committee

A steering committee that includes a subset of investigators in this study and representatives from Millennium will be formed to advise on the conduct of the study and development of publications and presentations (see also Section 12).

9.1.1 Drug Safety Monitoring Board

In accordance with Millennium standard procedures each clinical trial is evaluated to determine if a Drug Safety Monitoring Board (DSMB) should be convened. Applicable regulation and guidance (including the guidance set forth by the FDA as described in the Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf) are used to evaluate each trial in terms of potential confounding factors that complicate evaluation of the study safety and/or efficacy data, and potential risks of the study design or treatment to study participants. A DSMB is not indicated at this time for this study given that Millennium's standards and processes, which include continuous review and evaluation of safety data reported from all participating sites through the conduct of the study, are appropriate for the ongoing monitoring of patient safety and data integrity. Further, as described in Section 9.1, a Steering Committee has been formed to advise on the conduct of the study. However, taking into consideration the evolving benefit/ risk profile of MLN9708, the decision to convene a DSMB could be taken any time during the conduct of study C16007.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).

- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- Is a congenital anomaly/birth defect.

- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03.[58] Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or

other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

All SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee (contact information provided below) by faxing the SAE Form within 1 working day after becoming aware of the event. All SAEs and serious pretreatment events (which include all deaths) must be reported whether or not considered causally related to the study drug or study procedures. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information*

CCI

[redacted]

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03.[58] The criteria are provided in the Study Manual and also are available online at http://ctep.cancer.gov/reporting/ctc.html.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious (which include all deaths), will be monitored throughout the study as follows:

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRFs. That is, if a patient begins a new antineoplastic therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started.

- Serious pretreatment events will be reported to Millennium Pharmacovigilance or designee from the time of the signing of the informed consent form (ICF) up to first dose of study drug, but will not be recorded in the eCRF.

- SAEs will be reported to Millennium Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Any SAE that occurs at any time after completion of the study and the designated follow-up period that the investigator considers to be related to study drug must be reported to the Millennium Department of Pharmacovigilance.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

11.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

11.3 Electronic Case Report Form Completion

Millennium or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk (CD) or other electronic media will be placed in the investigator's study file.

11.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

11.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

11.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The

method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

11.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 Investigator Compliance

The investigator will conduct the study in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium, or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the study site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of

the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

11.11 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact PPD (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

For Product Complaints, call PPD at 1-877-TAKEDA7 (1-877-825-3327) or 1-919-666-9442 E-mail: medicalinformation@tpna.com

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to [redacted] (refer to section 10.2).

11.12 Closure of the Study

Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical study results will be submitted to the competent authorities and IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients

- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

Within 15 days of premature closure, Millennium must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

11.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

12. USE OF INFORMATION

All information regarding MLN9708 supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used

toward the development of MLN9708 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical study results pursuant to the terms contained in the applicable Clinical Trial Agreement.

A Steering Committee that includes a subset of investigators in this study and representatives from Millennium will be formed to advise on the conduct of the study and development of publications and presentations. This policy may be changed with the agreement of both the investigators and Millennium.

13. INVESTIGATOR AGREEMENT

I have read Protocol C16007, Amendment 6: An Open-Label, Dose-Escalation, Phase 1 Study of the Oral Formulation of MLN9708 Administered Weekly in Adult Patients With Relapsed or Refractory Light-Chain (AL) Amyloidosis Who Require Further Treatment

I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

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15. APPENDICES

15.1 Equation to Estimate Glomerular Filtration Rate (eGFR)

Race and Sex	Serum Creatinine Level µmol/L (mg/dL)	Equation
Black		
Female	≤ 62 (≤ 0.7)	$GFR = 166 \times (SCR/0.7)^{-0.329} \times (0.993)^{age}$
	> 62 (> 0.7)	$GFR = 166 \times (SCR/0.7)^{-1.209} \times (0.993)^{age}$
Male	≤ 80 (≤ 0.9)	$GFR = 163 \times (SCR/0.9)^{-0.411} \times (0.993)^{age}$
	> 80 (> 0.9)	$GFR = 163 \times (SCR/0.9)^{-1.209} \times (0.993)^{age}$
White or Other		
Female	≤ 62 (≤ 0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{age}$
	> 62 (> 0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{age}$
Male	≤ 80 (≤ 0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{age}$
	> 80 (> 0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{age}$

Source: Levey et al, 2009 [(60)]

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR – glomerular filtration rate

Expressed for specified race, sex, and serum creatinine level. To convert GFR from mL/min/1.73 m^2 to mL/sec/1.73 m^2, multiply by 0.0167. We derived equation coefficients from pooled development and internal validation sets. The CKD-EPI equation, expressed as a single equation, is $GFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female] × 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females ans 0.9 for males, α is -0.329 for females and -0.411 for males, and min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. In this table, the multiplication factors for race and sex are incorporated into the intercept, which results in different intercepts for age and sex combinations.

15.2 Amyloid Typing

Because clinical presentations are similar for the common types of systemic amyloidosis, the stigmata of organ involvement do not enable one to deduce the type of amyloid in a given patient.[(61)]

Two potential precursor proteins can co-exist in a patient, making it perplexing as to which type the patient has, a happenstance particularly relevant to 3 situations:

1. African-Americans who have higher rates of monoclonal gammopathies and a 4%

incidence of an hereditary ATTR variant (Val122Ile);[61, 62]

2. Patients presenting with peripheral neuropathy as the only clinical feature of organ involvement and a monoclonal gammopathy; peripheral nervous system involvement is a common presentation of hereditary disease;[62]
3. Elderly men who also have higher rates of both monoclonal gammopathies and wild-type ATTR.[62]

For diagnosis, tissue biopsy, either of an involved organ or a surrogate site (eg, abdominal fat), must demonstrate amyloid deposition by classic Congo red staining or electron microscopy.

For typing, immunohistochemical staining is frequently unreliable and inaccurate, and immunogold electron microscopy (IEM) reliable but limited by serologic dependence.[62] DNA sequencing of genes related to hereditary variants is useful for typing, particularly in African-Americans and patients with peripheral neuropathy as above (situations 1 and 2 where sequencing the transthyretin gene is indicated), or if adequate biopsy material for proteomic studies cannot be obtained. DNA sequencing is also useful for confirming proteomic findings and for subsequent screening of kin.[62]

Proteomics employing mass spectrometry with customized bioinformatic assessment of the constituents of the Congophilic deposits is now the gold standard for typing amyloid, enabling precise identification of type. It is specifically indicated for typing in cases where two potential amyloid precursor proteins may be present in a patient as in situation 3 above.

15.3 Eastern Cooperative Oncology Group Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[63]

15.4 New York Heart Association Classification of Cardiac Disease

The following table presents the New York Heart Association classification of cardiac diseases.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

15.5 Steroid Equivalent Doses

Approximately equivalent doses:

Steroid	Glucocorticoid Anti-inflammatory (mg)	Mineralicorticoid (mg)	Half-life (hours)
Cortisone	100	100	8–12
Hydrocortisone	80	80	8–12
Prednisone	20	100	12–36
Prednisolone	20	100	12–36
Methylprednisolone	16	no effect	12–36
Dexamethasone	2	no effect	36–72

Source: Knoben JE, Anderson PO. Handbook of Clinical Drug Data, 6th ed. Drug Intelligence Pub, Inc. 1988.[64]

CCI

[redacted]

CCI

[redacted]

15.7 Amyloid-Related Organ Involvement

Renal	Albuminuria >0.5 g/day in a 24-hour urine collection
Cardiac	The presence of a mean left ventricular wall thickness on echocardiogram >12 mm in the absence of a history of hypertension or valvular heart disease, or of unexplained low voltage (<0.5 mV) on the electrocardiogram; or NT-proBNP > 332 ng/L in the absence of renal failure (eGFR <45 mL/min/1.73 m^2). Clinical status is based on history, physical examination, and New York Heart Association (NYHA) heart failure class. Patients who are NYHA class 1 with evidence of cardiac amyloid by echocardiogram or electrocardiogram are categorized as having asymptomatic cardiac instability. Patients who are NYHA class 2 or higher with evidence of cardiac instability are categorized as having dominant cardiac instability (amyloid cardiomyopathy).
Hepatic and gastrointestinal	Hepatic involvement is defined as hepatomegaly on physical examination with an alkaline phosphatase value >1.5 × ULN. Gastrointestinal involvement is defined as direct biopsy verification of amyloid with symptoms such as gastrointestinal bleeding confirmed by tissue biopsy and diarrhea > 4 stools/ day over patient's baseline.
Autonomic and/or peripheral neuropathy	Neuropathic involvement is defined based on clinical history, autonomic dysfunction with orthostasis, symptoms of nausea or dysgeusia, gastric atony by gastric emptying scan, diarrhea or constipation, or abnormal sensory or motor findings, or both, on neurological examination.
Soft tissue and lymphatic	Involvement may be ascertained based on classic physical examination findings (macroglossia, shoulder pad sign, raccoon eyes, carpal tunnel syndrome, synovial enlargement, firm enlarged lymph nodes) or biopsy.

15.8 Assessment of Hematologic Disease Response

The definition of hematologic response to treatment is based on the difference between the concentration of amyloid forming (involved) and uninvolved free light chain (dFLC).

To be measurable dFLC must be at least 50 mg/L. Patients with dFLC < 50 mg/L are eligible for clinical studies but are evaluable only for complete remission.

Complete Response (CR)	Serum and urine negative for monoclonal protein by immunofixation; or free light chain ratio normal. <5% plasma cells in bone marrow without clonal dominance
Very Good Partial Response (VGPR)	dFLC < 40 mg/L
Partial Response (PR)	Reduction in dFLC > 50%
Progressive Disease (PD)	Is a 50% increase in serum M-protein to >0.5 g/dL from nadir/baseline, or 50% increase in urine M-protein to >200 mg/24 hours with a visible peak present; free light chain increase of 50% from nadir or baseline to >10 mg/dL (100 mg/L) Following a response of CR, the appearance of any detectable monoclonal protein by immunofixation, or abnormal free light chain ratio (light chain must double)

Source: Gertz et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): A consensus opinion from the 10th International Symposium on amyloid and amyloidosis [54]
Modified criteria proposed by the 2010 International Society of Amyloidosis Consensus [55, 56]

15.9 Criteria for Treatment Response of Amyloid-Related Organs

Response	Disease Progression[a]
Heart	
NT-proBNP reduction ≥ 30% and ≥ 300 ng/L in patients with eGFR ≥ 45 mL/min/1.73 m^2; baseline NT-proBNP must be at least 650 ng/L to be measurable, or	NT-prBNP increase ≥ 30% and ≥ 300 ng/L in patients with eGFR ≥ 45 mL/min/1.73 m^2 , or
A decrease in mean interventricular septal thickness by 2 mm, or	An increase in interventricular septal thickness by 2 mm compared with baseline, or
20% improvement in ejection fraction, or	An increase in NYHA classification by 1 class with a decrease in ejection fraction of at least 10%
Improvement in NYHA classification by 2 classes without an increase in diuretic use, and no increase in wall thickness	
Kidney	
At least a 50% decrease in 24-hour urine total protein (urine protein must be > 0.5 g/24 hours before treatment) in the absence of a reduction ≥ 25% in eGFR and a 0.5 mg/dL increase in serum creatinine	50% increase (at least 1 g/day) in 24-hour urine total protein to > 1.0 g/24 hours or
	25% worsening of serum creatinine or creatinine clearance (or eGFR).
Liver	
At least a 50% decrease in abnormal alkaline phosphatase value	50% increase in alkaline phosphatase value as compared with the lowest value, or
Decrease in liver size of at least 2 cm assessed in individual patients either by physical exam or radiographically. (Note: The same evaluation [physical examination or radiography] must be used consistently in individual patients throughout the study)	An increase in liver size by at least 2cm (radiographic determination)
Nerve	
No reliable method for defining peripheral and autonomic nervous system response.	Progressive neuropathy (peripheral, cranial or autonomic) not attributable to MLN9708 in the opinion of the investigator
Improvement in clinical examination findings	
Decrease in the reported Neurotoxicity score[a]	
Improvement in orthostatic blood pressure	
Improvement in any symptoms and/or signs related to peripheral	

neuropathy, cranial neuropathy, or other autonomic dysfunction	
Decrease is neuropathic pain	
GI	
Reduction of diarrhea to less than 50% of previous movements/day or decrease in fecal fat excretion by 50%	Worsening of diarrhea with increase > than 50% of previous movements/ day not attributable to MLN9708 in the opinion of the investigator or fecal fat by 50%

Source: Gertz et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): A consensus opinion from the 10th International Symposium on amyloid and amyloidosis. Am J Hematol 2005; 79: 319-328[54]
Modified criteria proposed by the 2010 International Society of Amyloidosis Consensus.[55]

a Organ progression can occur in an organ that has not been involved at baseline.

b Based on NCI CTC Version 4.02 criteria.[65]

15.10 Amendment 4 Rationale and Purposes

Rationale for Amendment 4

The purpose of this amendment is to provide information relevant to allowing patients to take study drug at home. Following agreement between the investigator and the sponsor, eligible patients may take study drug at home as directed.

An additional purpose of this amendment is to clarify male contraceptive requirements following the last dose of MLN9708. Previously, the protocol indicated that 30 days was a sufficient period of time for males to use effective methods of contraception. Considering spermatogenesis is 90 days and the half life of MLN9708, the sponsor advises male patients to practice effective barrier contraception or abstinence during the entire study treatment period and through 4 months after the last dose of study drug.

This amendment also provides additional revisions and corrections made to clarify the initial intent of sections as detailed below.

Purposes:

- Provide information relevant to allowing eligible patients to take study drug at home as directed
- Update male contraceptive requirements
- Clarify pharmacokinetic and pharmacodynamic sampling language
- CCI [redacted]
- Update the anticipated duration of study based upon current patient accrual data
- Clarify the starting dose level
- Revise planned Dose Level 3 from 5.2 mg to 5.5 mg
- Add information to the clinical experience summary regarding a patient in Study C16001 who received a dose of MLN9708 higher than was planned per protocol
- Add prophylaxis against risk of infection to the management of clinical events recommendations
- Clarify that a bone marrow aspirate and biopsy may be repeated at the discretion of the investigator as clinically indicated, but is not required during the follow-up period
- Distinguish between investigational (ie, MLN9708) and noninvestigational (ie, dexamethasone) medicinal agents
- Update reference to the Millennium clinician (previously referred to as medical monitor)
- Correct typographical errors, punctuation, grammar, and formatting

15.11 Amendment 5 Rationale and Purposes

Rationale for Amendment 5

This amendment allows for the following: a longer follow-up period for overall survival, an extension for a rollover study should one become available, and flexibility in laboratory evaluations as per standard of care.

Purposes for Amendment 5

The purposes of this amendment are to:

- Update the cover page with current signatories
- Update the duration of the study and overall survival time point
- Update the hematology and chemistry laboratory evaluation schedule
- Update the SAE reporting contact information
- Update the product complaint reporting contact information
- Correct typographical errors, punctuation, grammar, and formatting

15.12 Amendment 6 Detailed Summary of Changes

THE PRIMARY SECTION(S) OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 6 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Purpose: Update the cover page with current signatories.

The primary change occurs on the cover page:

Formerly read: ~~Chair,~~ Clinical ~~Review Board~~ (or designee)

~~Vice President~~, Oncology Clinical Research (or designee)

Now reads: PPD

Purpose: Update the duration of the study and overall survival time point.

The primary change occurs in Section 4.3, Duration of Study:

Formerly read: It is anticipated that this study will last for approximately ~~48~~ months. The duration of follow-up for overall survival will be ~~2 years~~ after the last patient enters the study.

Now reads: It is anticipated that this study will last for approximately **84** months. The duration of follow-up for overall survival will be **60 months** after the last patient enters the study. **Treatment may be continued in this study or in a MLN9708 rollover study, if and when such a study is made available, upon request by the investigator and agreement by the project clinician.**

Sections that also contain this change are:

- PROTOCOL SUMMARY
- Section 7.5.17, Follow-Up Assessments (PFS and OS)

Purpose: Update the hematology and chemistry laboratory evaluation schedule.

The primary change occurs in Section 7.5.10, Clinical Laboratory Evaluations:

Added text: **After 24 cycles on treatment, hematology and chemistry laboratory evaluations may be done to monitor the patient according to standard clinical practice per the treating physician.**

The Schedule of Events also contains this change.

Purpose: Update the SAE reporting contact information.

The primary change occurs in Section 10.2, Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Formerly read:

SAE Reporting Contact Information*

~~PPDI Pharmacovigilance (~~US and Canada~~)~~
~~24-hour helpline:~~ 800-~~201-8725~~
~~Fax: 888-488-9697~~

~~PPDI Pharmacovigilance (Central and South America)~~
~~24-hour helpline: +55 11 4504 4801~~
Fax: ~~+55 11 4504 4802~~

~~PPDI Pharmacovigilance (All other countries)~~
~~24-hour helpline: +44 (0) 1223 374240~~
Fax: ~~+44 1223 374102~~

Now reads:

SAE Reporting Contact Information*

CCI

[redacted]

Section 11.11, Product Complaints, also contains this change.

Purpose: Update the product complaint reporting contact information.

The primary change occurs in Section 11.11, Product Complaints:

Formerly read:

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact CCI (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

CCI

Now reads:

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact **PPD** (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

For Product Complaints, call **PPD** at
1-877-TAKEDA7 (1-877-825-3327)
or 1-919-666-9442

E-mail: medicalinformation@tpna.com

Purpose: Correct typographical errors, punctuation, grammar, and formatting.

These changes are not listed individually.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
PPD	Clinical VP Approval	23-Dec-2014 19:36
	Clinical Approval	24-Dec-2014 13:52